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MEDICAL ASPECTS OF ATOMIC ENERGY

by

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PHYSICAL INTRODUCTION

When at the beginning of this century, some prominent physicists, remost among them Ernest Rutherford, discovered that the radioactive elements are not stable but change continuously, and when in 1906, Rutherford and Boltwood stated that a continuous series of transformations leads from uranium to radium and, finally, to lead, the doctrine of the immutability of elements suffered a severe shock, yet still, all the other elements seemed firm like rocks and science went on building on the assumption that non-radioactive elements are absolutely stable. In fact, at the annual meeting of the British Association in 1907, Lord Kelvin reiterated the impossibility of transforming elements.

In 1919, however, Rutherford, by then Nobel Laureate and the leading physicist of his time, performed a feat which upset the fundamental concepts of matter, by bombarding nitrogen with alpha particles: he knocked hydrogen atoms out of it, he concluded from radioactive data that nitrogen consisted of helium and hydrogen (cf Evans, 1943).

The dream of the alchemists, who probably since the times of old Egypt attempted the transformation of elements, had become reality. Nitrogen, one of the apparently simplest, least problematic elements, as proved to consist of other elements. These and many other discoveries, to mention only the splitting of the lithium atom by Joliot-Curie and Walton (1932), led to the present, generally accepted doctrine that every atom, which since John Dalton (1808) seemed the smallest, indivisible particle of matter, is a universe by itself, "a miniature solar system" (Rutherford, 1911). It consists of a firm, more or less heavy and stable nucleus, charged with positive electricity, surrounded by a cloud of electrons, each of which is equal to one unit of negative electric energy and represents the smallest amount of mass existing. The positive charge of the nucleus which is equal to the negative one of all the electrons surrounding it is due to protons and positrons forming part of it, whereas another part of its mass consists of neutrons. Protons, each 1840 times the mass of an electron are deeply embedded in the atomic core and responsible for its "heaviness." Positrons discovered by Anderson (1931), are the long sought for

counterpart of the electron, having the same mass and the same amount of electric charge, viz., one unit of positive electric energy. Positrons and protons, being both positively charged, would repel each other if they were not cemented together by neutrons.

Neutrons predicted by Rutherford since 1920, were discovered by Chadwick in 1932, and proved of special importance for the following events. Neutrons are invisible minute fundamental particles, free of any electric quality, just simple matter, and yet, possessed of a tremendous energy, when split off from the nucleus.

It was known by then that permanent transformation of elements was due to alterations of their nucleus and that such alterations could be achieved by bombarding the atom with various fundamental particles. Due to their electric neutrality neutrons are neither attracted nor repelled by electric energy, therefore they proved the most suitable microbombs best fitted to penetrate the electron cloud and to hit the core proper, splitting off parts of it and so changing its physical character without altering its chemical individuality, in other words, transforming it into an *isotope*.

Some elements are having several isotopes. All of them have got the same nuclear charge which makes them chemically alike, but each has got a different nuclear mass, expressed by a different atomic weight which is responsible for their physical differences.

Fermi, the famous Italian physicist, using this method, had succeeded by 1934 in transforming a large number of elements. Two years later (1936) E. O. Lawrence and Cooksey in America, announced the invention of the cyclotron which permits the production of streams of hydrogen, deuterium and helium nuclei, which possessed of a kinetic energy of several million electron volts, are used to bombard other atoms, producing on a large scale isotopes, some of which are *radioactive*. The radio-active isotopes in addition to having an altered atomic weight, emit rays, this is due to their unstable nucleus. They are the result of transformation of elements. So, tellurium bombarded with deuterium yields radio iodine 131, or nitrogen bombarded with "slow" neutrons can be converted into radio carbon 14.

A further decisive step in the history of nuclear physics was the bombardment of uranium with neutrons in 1939. Otto Hahn at the Kaiser Wilhelm Institute in Berlin, found that one of the products of so treated uranium was radioactive barium, the Viennese lady-physicist Lisa Meitner concluded that this must be due to splitting the uranium atom into two almost equal halves, a phenomenon called *fission*.

When, finally, it was discovered that such fission is regularly accompanied by splitting off two or three more neutrons from the uranium nucleus than are required to achieve fission, it became apparent that this surplus of ejected neutrons could produce fission of other uranium atoms until a self-perpetuating *chain reaction* would release enormous amounts of energy. It was calculated that fission of all atoms contained in one pound of uranium would produce 10,000,000 kilowatt-hours.

Soon after, common uranium 238 was replaced in fission experiments by its isotope uranium 235 and by plutonium 239. Fission of these much less stable nuclei produced a tremendous explosive release of

nuclear energy, a discovery which, according to nuclear physicists, made the invention of the atomic bomb inevitable

THE ATOMIC BOMB

Whether the actual use of this weapon in warfare was right or wrong, future historians will have to decide. We are concerned with the results of its application on human beings and they are impressive enough (Le Roy, 1947). In Hiroshima, where a uranium bomb was used, out of a population of 3 lakhs, 80,000 died and 40,000 were injured, in Nagasaki, a plutonium bomb killed 40,000 and injured 25,000 out of 2,00,000. When the bomb was released, Hiroshima had 150 physicians of whom 65 were killed outright and most of the others so badly injured that they were unable to treat others. Of 1780 nurses, 1654 were killed or hurt too severely to carry on. But on the day of the bombing 85,000 in Hiroshima and 50,000 in Nagasaki required medical aid, of which there was hardly any available.

The atomic bomb exerts its destructive effect by releasing energy of four different kinds—mechanical power, heat, light and ionizing radiation.

The *mechanical energy* was sufficient to crush reinforced concrete structures in the centre of its effect, steel-framed factories at a distance of 4,700 feet and to demolish the Japanese type of wooden houses at a radius of 8,000 feet, roof tiles were blown off as far as 3.5 miles from the site of the explosion.

The *heat* caused burns of the flash type, that is only in the direct line of sight between bomb and victim, but it was so intense that burns were inflicted at distances of 13,000 feet and every inflammable object up to a distance of 11,000 feet was scorched or set on fire.

The *light* was comparable to sunlight concentrated by a burning glass.

For the future course of medical investigations of the greatest importance were the effects of *radiation*, due, particularly, to the effect of gamma rays, deeper penetrating than any known until then. The fate of those suffering from "radiation injury" depended upon the dose of radiation received and this was in inverse proportion to the square of distance, and dependent on the kind of material which protected the victim at the time of explosion, whether it was wood, earth, bricks, concrete, etc.

Most of those affected by radiation, experienced nausea and vomiting of short duration a few hours after the bombing. Those who received the greatest dose of radiation without any other injury, fell ill on the day after the explosion, suffering from fever, diarrhoea and, 4 to 7 days later, from purpura which preceded sudden death by a short time, their blood showed frequently a total lack of leucocytes and thrombocytes—A smaller dose of gamma rays caused symptoms to appear after one to four weeks. Loss of hair, severe diarrhoea, purpura, fever, leucopenia and anaemia were constant features in the majority of radiation victims. The quickly progressing signs of blood destruction and failing blood regeneration caused ulceration of all the mucous membranes as seen in agranulocytosis, epistaxis, melaena, haematuria, and metrorrhagia occurred regularly and resistance to secondary infections decreased to an alarming extent, especially in wounded or burned patients. The number of leucocytes was always below 1,500

and sometimes reduced to 100, consisting only of lymphocytes. Japanese physicians stated that of those so affected 100 per cent died but with early intensive treatment the mortality rate might have been reduced by 25 to 50 per cent. The least severe affected showed loss of hair three to five weeks after the explosion, all the other symptoms were proportionately milder, leucocyte counts were above 1,500 but anaemia and thrombocytopenia dominated the blood picture. In addition, complete sterility was noted in men while the female generative organs were much less affected.

In accordance with the clinical observations, post mortem examinations showed that the worst affected part of the human body were the blood building organs, bone marrow, lymph glands and spleen on the one hand, the gastro-intestinal tract with widespread ulcerations and the atrophied testes on the other. In the worst damaged cases the bone marrow showed complete disappearance of all erythropoietic and myelopoietic elements. In the less severely irradiated groups regeneration started within seven to ten days, producing after 3 to 4 weeks macrophages, plasma cells and lymphocytes, in some cases even hyperplasia became apparent. Spleen and lymph glands were found completely stripped of lymphocytes, only the stroma remained. Here regeneration was much slower and even months after the radiation injury was suffered, only a fraction of the normal amount of lymphocytes was present. The testes contained no spermatozoa and the tubules were replaced by proliferating Sertoli cells.

Death was due either to intractable diarrhoea with dehydration and acidosis, to pneumonia, septicaemia and other infections, consequences of low resistance due to leuco-and, especially, granulocytopenia or to various haemorrhages due to diminished thrombocytes. In the worst affected group, 60 per cent died of subarachnoid haemorrhage. Thus, the essential features of atomic radiation injuries are similar to those found following overdosage of Roentgen rays, especially seen in dogs purposely exposed to heavy overdoses.

Treatment consists in blood transfusions, penicillin, liver extract, pentnucleotide, large doses of vitamin B₆ (pyridoxine) and careful protection against secondary infections.

Apace with the spectacular investigations which led to the construction of the atomic bomb went attempts to use atomic energy for constructive purposes. In 1934, Joliot and Curie discovered that radioactivity could be artificially induced in various elements. The cyclotron and especially, the fission pile now are producing such artificially radioactive substances, the *radio-isotopes*, on a large scale. A fission pile consists of uranium or plutonium rods, separated from each other by insulating graphite, the elements to be transformed are bombarded with neutrons, derived from the uranium or plutonium, the former produces "slow," the latter "fast" neutrons. Radio-isotopes are used in medicine either as tracer elements for research or as carriers of radiation, substituting x-rays or radium, for purposes of treatment.

It may be mentioned here that x-rays, radium and radio isotopes are not the only sources of medically important radiation. *Cosmic rays*, to which we are exposed continually, apparently have got some influence on the development of cancer. Mice of a strain of which

the spontaneous frequency of mammary tumour occurrence was well known, have been kept under lead plates which intensify cosmic radiation. Those so exposed to a higher than normal dose of cosmic rays, developed malignant tumours in a percentage significantly higher than controls (cf Edit, 1947). It was even suggested that only such chemical compounds act as carcinogenic agents which are capable of converting cosmic and similar penetrating radiation into a form of energy which can induce cancer (Figge, 1947).

THE TRACER TECHNIQUE

Induced radioactivity which can be imparted to every element provided biologists with new tools for research. It seems no exaggeration to say that the tracer technique, based on radio-isotopes as tracer elements and on the Geiger counter, represents the greatest progress in biological research methods since the invention of the microscope and the discovery of Roentgen rays.

Roentgen rays make visible every object inside the body which is impenetrable to them or radio opaque, the tremendous importance of this achievement needs no emphasis but the fact that x-rays permit only observation of radio-opaque material and of particles big enough to be visualized marks their limitations.

The new tracer technique widened scope and range of biological research as much as the new conceptions of atomic structure deepened the understanding of the nature of matter. It makes possible the following up of every atom which emits ionizing radiation. If we want to know, for instance, what are the destinies of calcium, iodine, phosphorus or iron in the human body, we have only to take their radioactive isotopes, to administer a measured quantity of any of them by mouth or by injection and to move a Geiger counter along the body surface or to introduce it in a body cavity (rectum, vagina, etc.). Wherever a radioactive particle is localized, be it in muscles or bones, liver or spleen, thyroid or kidneys, the Geiger counter signals its presence and the intensity of its radiation, so that one knows exactly not only where the tracer element is at any moment but also how much of it is there. For tracer purposes such extremely weak activities are used that there is no biological effect due, to radiation.

An additional advantage of the greatest importance is that these radioactive elements are chemically identical with their natural, inactive brothers. Radioactive phosphorus, for instance, is treated by our body and behaving in our system exactly as ordinary phosphorus does so that every observation made regarding a radio-isotope is true also for the natural element.

Their radioactivity, on the other hand, imposes some limitations on the application of tracer elements. Radioactivity decreases in course of time and every radioactive substance is characterized by the speed with which it loses its ionizing capacity. The time it takes for half the atoms of any given element to exhaust their radioactivity is called its "half-life" or "half-period" which varies from several billion years for uranium and 1,700 years for radium, to 12 hours for radio-iodine 131 and a few seconds for certain emanations.

For experimental and therapeutic purposes only elements with a short half-life can be used because body tissues must not be exposed to radiation for too long a period.

phosphorus equal to, but not better than, that of X-rays. Quite recently Belding and Ross (1947) expressed their opinion that in the future radiophosphorus would replace X-rays in the treatment of chronic leukaemias, due to the absence of radiation sickness, the longer period of survival observed in patients treated this way and the fact that the new method is less expensive and can be carried out anywhere.

Radiophosphorus had no effect on acute leukaemias and Hodgkin's disease. Multiple myeloma was not prevented from growing or spreading but the severe pain caused by it was considerably relieved.

It must be borne in mind that radio-phosphorus, like X-rays, has a tendency to depress the production of erythro-, leuco- and thrombocytes alike, so that while treating polycythaemia, one has to watch for leuco- and thrombocytopenia, while application of radiophosphorus in leukaemias might produce anaemia and reduce the platelets, the period of latency for the manifestation of any of these untoward after-effects being from two weeks to ten months. However, Hall et al (1947) state that in their cases none of these effects were dangerous or lasted for more than eight weeks. Neither toxic phosphorus effects nor radiation sickness was observed.

Quite recently Platt (1947) sounded a note of warning, as he found in normal tissues of subjects, treated with radiophosphorus, pathological mitoses, formation of giant cells and some depressive effects on testes and ovaries, not previously reported.

An interesting therapeutic experiment was reported by Muller (1947). He injected *radio-zinc* locally into nodes of secondary carcinomatous dissemination of the peritoneum and observed some promising regressive changes.

The results of therapeutic applications of radio-isotopes so far have been encouraging but not spectacular. We must not forget, however, that we are standing only at the beginning of a development which has hardly started due to the great scarcity of radioactive drugs. With the construction of the new giant cyclotron at California University numerous fission piles working for medical research institutions in the U.S.A. and the invention of the "fast reactor" soon new results should be expected, especially in the field of cancer therapy.

In India, we have every hope that the Tata Institute of Fundamental Research under the directorship of the brilliant physicist H. J. Bhabha would soon take up the production of medically useful radio-isotopes, the more so as the thorium found in Travancore provides material for manufacturing uranium 233.

Apart from the difficulty to obtain sufficient radioactive isotopes for research and treatment, which up to quite recently hampered work on a broad base even in the U.S.A., manufacturing on a large scale is restricted also by the danger accompanying the handling of this material, risks of which we are as yet only very incompletely informed, and which are sadly underrated by nuclear physicists themselves. One of the most serious drawbacks in the investigation of radiation effects is their long period of latency, particularly, their cumulative effect on the chromosomes of the sex cells of those who due to their profession are exposed to radiation for a long time may become manifest only in the next generation. The full utilization of atomic energy might, therefore, not be possible until one knows much more about ways and

means of protection. What might be expected, once these preliminary problems are solved, could be guessed from the fact that the atomic bombs of the last war utilized only 0.1 per cent of the energy contained in the mass of uranium or plutonium exposed to fission, the potential energy of one pound uranium (U^{235}) being equal to that of 1,500 tons of coal.

Surveying these results, incompletely reported though they are, there cannot be any doubt that at present the utilization of atomic energy for destructive purposes by far outweighs that for constructive ones; this might be due either to an innate trend of human nature or to the fact that the development of nuclear physics got a tremendous impetus under war conditions and developed much quicker than most scientists anticipated so that there was not sufficient time to work out safeguards. In an essay on unsolved problems of science, published in 1940, J. B. S. Haldane remarked "a few years ago we used to read sensational stories about what would happen when atoms were split. A single bomb would liberate enough energy to destroy a whole city."

"Unfortunately the prophets had forgotten to do a few little calculations. I am an optimist, and I hope that within a century it will be possible to construct a motor using atomic energy, it will probably weigh a ton and develop several mouse-power." A foot-note, added apparently later, concedes that "this due to recent work on uranium may be sooner than I thought." And Haldane is a well informed, leading scientist.

Whatever the reasons, we have to face the fact that never before in history mankind was living under such a threat of possible extinction as it does to day, made possible by an array of destructive forces unleashed by man himself in his search for knowledge, not directed and not limited by a sense of responsibility, based on ethical considerations or religious convictions.

Dr Fosdick, president of the Rockefeller Foundation, characterized this situation clearly enough when he said "The pursuit of truth has at last led us to the tools by which we can ourselves become the destroyers of our own institutions and all the bright hopes of the race," and Albert Einstein expressed the frailty of our present hopes by saying "Science has brought forth this danger, but the real problem is in the minds and hearts of men,"—frail hopes, but still some hope.

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*This paper contains many references to literature on radio-phosphorus

**This is the 6th report on radio-iodine therapy published by these authors since 1942

ACUTE CORONARY OCCLUSION

A STUDY OF 82 CASES WITH SPECIAL REFERENCE TO SOME LESS KNOWN FACTS

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A little more than a century of medical progress intervened between the classical description of Angina Pectoris given by Heberden before the august body of the Royal College of Physicians in 1768 and the demonstration of sudden occlusion of the coronary artery, as the cause of death, by Hammer at an autopsy performed in 1876. From then onwards it was held by the medical profession that sudden occlusion of a coronary artery was incompatible with life and resulted in instantaneous death. The credit for dispelling this belief goes to James B. Herrick who was first to think that a few hours or even a few days of life were possible in spite of occlusion of a coronary artery. He first made this diagnosis in a case which lived for 52 hours after an attack of what seemed like an acute abdominal catastrophe, but was not quite that. It was after the patient's death, on the 18th January 1910, that Herrick suggested to his friend who performed the autopsy that the cause of the attack would probably be a thrombus in one of the coronary arteries. True to the prediction, a thrombus was found in the left coronary artery with an area of infarction in the anterior wall of the left ventricle. Herrick reported this interesting case before the Association of American Physicians on the 14th May 1912 and later published his paper on 'Clinical features of sudden obstruction of the coronary arteries' in the J A M A¹. This paper did not receive the attention Herrick expected so important an announcement to receive. In his own words 'it fell like a dud'. Undaunted, Herrick carried on an intensive personal propaganda about the existence of this clinical entity before his students, his internes and his colleagues incessantly but it was not until the publication of his second paper² on Coronary Thrombosis in 1918 that the American physicians at the bedside and in their learned discourses took to thinking seriously about this diagnosis. In England the diagnosis was not seriously thought of before 1925 and suffice it to say that a physician of the great standing of Osler had obtained the Fellowship of the Royal College of Physicians of London before he had come across a case of even Angina Pectoris. But ever since 1925, men of medicine all over the world, where western influence predominates, have thought more and more of the coronary arteries and their diseases and angina pectoris no longer remains an exclusive disease for the seniors to discuss as Osler³ had thought only 87 years ago.

Nomenclature There has been some confusion and a good deal of controversy regarding the use of such terms as coronary thrombosis, coronary occlusion, acute coronary occlusion, acute coronary insufficiency, myocardial infarction etc in literature. It is extremely difficult

A paper read before the 72nd Meeting of the G S Medical College and K E M. Hospital Staff Society Bombay on July 12, 1947, with Dr Hameed in the chair

to select a term which would be absolutely correct for every case of what may be called the coronary syndrome. The term coronary thrombosis is a time-honoured one and was fairly extensively used till it was shown by Patterson⁴ and by Horn and Finkelstein⁵ that the commonest mechanism of occlusion of the coronary arteries was through subintimal haemorrhage. Blumgart and his colleagues⁶ object to the term coronary occlusion as being only a pathological entity for there may be occlusion without any clinical manifestation. They suggest the use of the term myocardial infarction for the symptom-complex of coronary occlusion, but it should be realised that every case of coronary occlusion does not produce an infarct, particularly if the occlusion is very gradual or if death is very quick.⁷ Master⁷ and his Mt Sinai band prefer the term acute coronary occlusion and reserve the term acute coronary insufficiency for the condition which results from sudden increase in demand on the heart which cannot be coped with.

In the present study the term acute coronary occlusion has been used as the most convenient one though some of the cases would, according to Master, be classified as acute coronary insufficiency.

The 82 cases here reported were admitted in the K E M Hospital, Bombay, during the years 1941 to 1945. Only those cases where the diagnosis was confirmed by a very typical clinical picture or an E C G or a necropsy have been recorded and all doubtful cases have not been taken into consideration.

Incidence There is an increasing feeling among the medical men that coronary disease is more frequent now than what it was 30 years ago and the statistics in the United States and England support this belief as shown by Sir Maurice Cassidy in his Harveian Oration for 1946.⁸ Unfortunately no such figures are available for India. It would be not out of place however to mention that such is also the experience of the senior members of the profession here. The yearly incidence in the recorded series is almost constant during the first four years but show a sudden rise during the fifth year as shown in Table I.

TABLE I Yearly Incidence

| Year | 1941 | 1942 | 1943 | 1944 | 1945 | Total |
|-------------|------|------|------|------|------|-------|
| No of cases | 11 | 11 | 17 | 18 | 30 | 82 |

Aetiology There is no one factor to which we can point as the cause of coronary occlusion though we can mention a number of factors which would predispose to coronary occlusion.

Age The age at which coronary occlusion is most common is the fifth decade and after. This has been the teaching for a long time but now the time has come when it needs modification. The barriers of age are gradually being broken down here as in the case of malignant diseases and even apart from embolic or syphilitic cases, coronary disease and angina pectoris are seen with an increasing frequency in the younger age groups. In 1928 Stolkind⁹ reported 4 cases of angina pectoris in children and collected 25 more from literature, a majority of these being rheumatic children. Smith and Bartels¹⁰ in 1932 reported 2 cases of coronary thrombosis of 35 and 36 years and could collect

only 20 cases of less than 40 years from the literature. In 1937, Durant¹¹ reported 7 more cases of 35 and under, and Glandy¹² and his colleagues reported 100 cases of coronary occlusion under the age of 40, 8 of them being less than 30 years old. French and Dock,¹³ in 1944, reported a series of 80 American service men between the ages of 20 and 36 years who had acute coronary occlusion, and Newmann¹⁴ in 1946 added a further 50 cases of English men and women in the services upto the age of 35, the youngest being a youth of 20 years, and 22 of them being less than 30 years old. Heilig¹⁵ mentions a case of a Parsi lad of 19 who had coronary occlusion. In this series is reported the case of a girl who was only 9 years old and who had attacks resembling angina pectoris with electrocardiographic evidences of posterior myocardial infarction. Holzer and Polzer¹⁶ report 16 cases between 28 and 40 years. Yet, a majority of cases of coronary occlusion are between 50 and 70 years old. From a series of 1000 cases of angina and coronary occlusion reported by Cassidy⁸ as many as 70 per cent were between 50 and 70 years. The average age of a group of 72 cases of coronary occlusion coming for necropsy was found to be 59 years by Mallory¹⁷ and his co-workers. The detailed age distribution, in the present series is shown in Table 2. The largest single age group is that of 38 patients (46.3 per cent) between 40 and 49 years. 20 cases (24.4 per cent) are below the age of 40.

TABLE 2: Age.

| Age Group | Below 20 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70 & over | Total |
|----------------------------|---------------|-------|-------|---------------|-------|-------|-----------|-------|
| No of cases | 1 | 3 | 16 | 38 | 15 | 8 | 1 | 82 |
| Percentage of distribution | 1.2 | 3.7 | 19.5 | 46.3 | 18.3 | 9.8 | 1.2 | 100 |
| | 24.4 per cent | | | 75.6 per cent | | | | |

Sex Coronary occlusion is predominantly a disease of the male though the proportion of male to female has varied within such wide limits as from 2.72 to 1 upto 49 to 1. The wide range may be explained by the fact that the different sources do not drain the male and female population in an equal proportion. The average incidence according to modern figures would work out somewhere between 3 to 5 males for every female. In the present series there were 78 males and 9 females bringing the proportion to 8.1 males for every female case recorded. The sex incidence from various sources has been shown in Table 3. It will be seen that the disease becomes more frequent in females past the age of 50.

TABLE No 3 Sex

| Author | 14 Newmann | 18 Osler | 19 Heberden | 12 Glandy et al | Parkinson & Bedford |
|------------------|--|-------------|----------------|---------------------------------------|------------------------|
| Nature of source | 50 service people under 35 years | Angina | Angina | 100 under 40, cases of Coronary | Coronary |
| M:F | 40:1 | 40:1 | 33:1 | 24:1 | 9:1 |

| Author | Present series | Smith et al 21 | White & Bland 22 | Holzer | Holzer 16 & Polz | Cassidy 8 |
|------------------|----------------------|-----------------------|------------------|-----------------------|-------------------------|---------------------------------|
| Nature of source | 82 cases of Coronary | 100 cases of Coronary | Coronary | 521 Coronary all ages | 16 Coronary of 23 to 40 | 1000 cases of angina & Coronary |
| M.F | 8 1 1 | 6 0 1 | 5 1 | 4 3 1 | 4 3 1 | 8 5 1 |

| Author | 3 Levine | Mallory et al 17 | 24 Fisher & Zukermann | Cassidy |
|------------------|----------|----------------------------|-----------------------|---|
| Nature of source | Coronary | 72 cases of fatal Coronary | 108 cases of Coronary | Angina and Coronary above the age of 60 |
| M.F | 8 5 1 | 2 8 1 | 2 72 1 | 1 1 4 |

Religion Apart from the influences of various environmental factors the incidence of coronary occlusion predominating in one particular sect may suggest a hereditary influence. Unfortunately our data is not adequate to draw any conclusions from this point of view but the incidence in different religions is shown in Table 4

TABLE 4 Communities

| Hindus | Muslims | Christians | Parsis | Jew | Total |
|--------|---------|------------|--------|-----|-------|
| 40 | 14 | 14 | 4 | 1 | 82 |

Family history A family history of some cardiovascular disease was obtained by Cassidy⁸ in as many as 50 per cent of his 1000 cases of angina and coronary disease. Other workers have not been so successful with the family history and the present study does not give any information of value in this direction.

Occupation Coronary occlusion is more common amongst the mental workers and therefore those who are socially on the higher rungs of the ladder. The various occupations pursued by subjects of this study are shown in Table 5

TABLE 5: Occupation

| | | | Not mentioned or retired | Total |
|--------------|----|-----------|--------------------------|-------|
| Clerk | 19 | Postman | 2 | |
| Labourer | 13 | Policeman | 1 | |
| Teacher | 2 | Engineer | 3 | |
| Tram driver | 2 | Cook | 2 | 27 |
| Motor driver | 1 | Housewife | 8 | |
| Fireman | 2 | Student | 1 | |
| | 39 | | 16 | 82 |

Build A fair proportion of the victims of coronary occlusion are of the hypersthenic type. Smith, Sauls and Ballew²¹ found that 35 per cent of their cases were definitely obese whereas French and Dock¹³ found 78 out of their 80 cases (90 per cent) to be overweight, 11 of them were very obese, 29 obese and 30 had extra weight. Newmann¹⁴ is

also of the opinion that obesity plays a part in the aetiology of coronary occlusion. In this study only 11 patients (13.42 per cent) were obviously obese.

Tobacco, alcohol and syphilis These factors have been held responsible time and again for coronary occlusion but a definite proof of their direct influence has never been given. Syphilis may at times be responsible for producing stenosis of the mouths of the coronary arteries but incidence of syphilis is not higher amongst the subjects of coronary occlusion than amongst the general population. In the present series only six cases (7.32 per cent) had either the history or the clinical or the serological evidence of cardiovascular syphilis. The Wasserman or the Kahn reaction was positive in only 3 cases. Similarly Holzer and Polzer¹⁶ found positive serological evidence of syphilis in only 4 per cent of their 521 cases and Fisher and Zukermann¹⁴ found that only 3 of their 108 cases had a positive W. R. and 2 more had history of syphilis though they were seronegative.

Hypertension In the literature the incidence of hypertension preceding coronary occlusion has varied from 33 per cent to 78 per cent. In Cassidy's⁸ series the incidence of hypertension was 55.4 per cent, Smith et al²¹ found hypertension in 41 per cent, Master²⁵ and his colleagues in 60 per cent, Fisher and Zukermann²⁴ found that 65.5 per cent of their female and 39.5 per cent of their male subjects of coronary occlusion had hypertension, Patterson²⁶ and Boas²⁷ presume a direct relationship between coronary thrombosis and hypertension. On the other hand in Newmann's¹⁴ series of younger subjects of coronary occlusion the incidence of hypertension was very low (6 per cent) and a similar low incidence in the younger subjects has been reported by Glendy Levine and Smith¹². Master et al²⁵ also find that the incidence of hypertension is 28 per cent at 25 years, and 80 per cent at 75 years and more. Incidence of hypertension also varies with the sex and besides the higher incidence in females found by Fisher and Zukermann²⁴ quoted above, Master²⁵ et al also found the incidence of 81 per cent in their female patients as against 64 per cent in males. They are of opinion that females rarely have coronary sclerosis unassociated with hypertension or diabetes. In the study under review 33 cases (40.3 per cent) had hypertension. Only 4 of the 20 cases below 40 years (20 per cent), and 5 of the 9 females (55.5 per cent) had hypertension. The figures of the various authors are summarised in the Table 6.

TABLE 6 Hypertension

| Author | Master et al 25 | | | Fisher and Zukermann | | | | Smith |
|-------------|-----------------|------------------|-----------|----------------------|-----------------|---------|-------|-----------|
| Incidence % | 81 | 80 | 69 | 64 | 28 | 65.5 | 39.5 | 41 |
| Remarks | Females | 75 yrs. and more | All cases | Males | 25 yrs and less | Females | Males | All cases |

| Author | Cassidy | Newmann | The present series | | | |
|-------------|-----------|----------------|--------------------|---------|-------|----------|
| Incidence % | 55.4 | 6 | 40.3 | 55 | 30 | 20 |
| Remarks | All cases | Cases below 35 | All cases | Females | Males | Below 40 |

Diabetes Diabetes is at times associated with coronary occlusion. Smith et al²¹ found its presence in 9 per cent, Master²⁵ et al in 11.2

per cent, and Mallory¹⁷ et al in 12.5 per cent. There were 8 diabetics in the present series. Probably the relation between diabetes and coronary occlusion is not different from that between diabetes and arteriosclerosis.

Cholecystitis Recently much has been talked about the gall bladder being in some way responsible for arteriosclerosis and coronary disease. A definite hypercholesterolaemia has not been shown in a majority of cases of coronary occlusion. The marked preponderance of coronary disease in the males raises a question whether the absence of cholesterol clearing mechanism, with which the female is endowed by virtue of her child bearing capacity, has anything to do with coronary occlusion, hypertension and arteriosclerosis. In their 100 cases Smith, Sauls and Ballew obtained a history of chronic cholecystitis in 9 cases only. In this series no data to this effect is available.

Chronic focus of infection, according to Holzer and Polzer¹⁸, is important in the production of coronary occlusion. Newmann¹⁴ believes that an evident source of infection may hasten the advent of atheroma as in one of his cases who had a persistent sinus following an infected gunshot wound.

Rheumatic infection Since the day that Karsner and Bayliss²⁸ reported changes resembling arteriosclerosis in the coronary arteries as a result of rheumatic infection, the aetiology of coronary occlusion in the young has assumed a different aspect. Newmann¹⁴ found a history of previous rheumatic infection in 8 of his 50 cases. Stolkind⁹ reports 29 cases of angina following rheumatic infection. The case of a girl of 9 reported in this series had history of repeated sore throat and joint pains with fever but there was no evidence of endocarditis.

Physical stress So far physical stress was not considered directly responsible for precipitating an attack of coronary occlusion but the sudden increase in incidence of coronary occlusion amongst the younger generation in the services makes one think whether the sudden enforcement of strenuous military life is in any way responsible for this sudden increase. In his series of 30 Newmann⁴ found that 11 developed the acute attack immediately after strenuous exertion, and 12 more within a few days. French and Dock¹³ report 15 cases as having had the attack during severe physical exertion and 26 more within 1 to several hours of exertion. 9 out of the 82 cases here presented gave a history of severe physical effort less than 24 hours prior to their attacks.

Mental stress "Worry more than physical stress", says Roger Lee, "is the baneful influence of life" and this is more true for coronary disease than for any other malady. Coronary occlusion is progressively being brought more and more in the ever increasing ambit of psychosomatic diseases and Arlow²⁹ makes bold to describe a coronary personality—an individual with mesochistic trend and a never ending compulsive striving for achievement and mastery. In the present series four cases had more than their usual share of mental stress immediately prior to their attacks.

Arteriosclerosis Arteriosclerosis is the one most important aetiological factor in cases of coronary occlusion of nonembolic or non-syphilitic origin. However it remains to be ascertained which of the factors bring about an occlusion of a sclerotic vessel and how do these factors operate. The ultimate aim of these studies is to be in a position

to foretell which sclerotic coronary is going to be in a position to be occluded and if so, why so, if not, why not? In this series definite evidence of arteriosclerosis was found in the fundi of eight cases and also in all the five necropsies available. In the remaining cases no special attempt was made *e g* fundus examination, to search for the evidence of arteriosclerosis.

Diet The effect of diet on coronary disease has not been sufficiently investigated to establish any definite opinion but it seems that the relation would be very much the same as in arteriosclerosis and hypertension. In the present series we find a comparatively high incidence of people taking a so-called mixed diet as shown in Table 7 but no presumptions are made on this slender evidence.

TABLE 7 Diet

| | |
|-------------|---------------------|
| Vegetarians | 17 (20.74 per cent) |
| Mixed diet | 65 (70.26 per cent) |

Precipitating factors We do not definitely know what factor or factors precipitate an attack of coronary occlusion. In contrast to angina pectoris the history of sudden strenuous physical exertion or mental stress immediately preceding the attack is, more often than not, absent. A majority of attacks occur during the early hours of the morning when the patient is in bed. Recently vascular spasm has been considered as an additional factor to mechanical obstruction in the production of coronary occlusion³⁰⁻³¹. Hence the precipitating factors of angina pectoris may be to some extent responsible, in a few cases at least, in bringing about coronary occlusion. Luten³¹ believes that such vasoconstrictor impulses travelling through the vagus originate in the gastrointestinal tract in relation to meals or ingestion of cold fluids. Some allergic influences have also been considered as possible precipitating factors but no definite conclusions have been arrived at so far.

Acute infectious fevers may precipitate coronary occlusion as shown by 2 cases of French and Dock¹³ and 3 cases in this series. In 2 of them the attack was brought on during the first week of convalescence from lobar pneumonia while the third one had attack of acute tonsillitis with fever for about 5 days which subsided just 2 days before the attack of coronary occlusion.

Post operative thrombotic phenomena may at times be the cause of coronary occlusion as reported in 3 of the 108 cases of Fisher and Zukermann,²⁴ who developed coronary occlusion within 2 weeks of operation.

Trauma It is doubtful if external trauma plays any part in production of myocardial infarction. Lemoff's²² observations in this respect are interesting. He records 18 cases of acute myocardial infarction due to non-penetrating injuries of the chest. 17 of these were industrial workers and one was a surgeon who got jammed against the steering wheel of his automobile. The diagnosis was made from history and signs of external injury. Lemoff labels these cases as 'acute traumatic heart disease with myocardial and pericardial damage' and believes that the infarction may be due to direct or physical bruising of the heart against the bony parts or to increased intraventricular tension due to blood being prevented from leaving the ventricles or forced back into the ventricles by compression.

(To be continued)

Critical Notes and Abstracts

PENICILLIN INHALATION THERAPY by MAURICE S. SEGAL and CLAIRE MACLANTYRE RYDER, (*New England Journal of Medicine*, January 23, 1946, 182-189) This report concerns a summary of our findings in the use of penicillin aerosol in the treatment of 85 patients with bacterial pneumonia, suppurative bronchitis, bronchiectasis, lung abscess, infective bronchial asthma, infective laryngotracheobronchial edema, chronic pulmonary emphysema and emphysematous blebs.

The sodium or calcium salt of penicillin was used. Generally 25,000 units of penicillin were dissolved in 10 cc of physiologic saline solution and given at three-hour intervals for six to eight doses daily.

The calcium salt was less irritating but usually more difficult to obtain than the sodium. Many patients objected to the taste and smell of the penicillin aerosol or found it irritating to the tongue or oropharynx. These complaints were minimized by a change to other lots of penicillin. A few patients developed sore tongues or stomatitis following the therapy. Saline rinses, dental hygiene and frequent sips of water during the treatment helped to diminish these complaints.

Recently we have noted local and generalized manifestations consisting of edema of the lips or the mucosa of the mouth and, in several cases, a generalized urticaria. The local reactions generally subsided after a change to another type of penicillin.

The apparatus used in our studies was the basic Vaponefrin nebulizer enlarged to a capacity of 2 liters to permit the utilization of the expired penicillin. This nebulizer produced a fine, voluminous mist or smoke screen with a particulate size of less than 1 micron. A piece of rubber tubing connected the nebulizer with a regulator attached to an oxygen tank. Oxygen flows of 5 to 7 liters were usually sufficient to aerosolize 10 cc of the penicillin solution in approximately 15 minutes. To avoid loss of the drug in expiration, a glass Y-tube was placed just proximal to the inlet of the nebulizer. The patient or the nurse was instructed to close the open end with a finger during most of the inspiratory cycle and to remove the finger at the end of inspiration and during the entire expiration. With this technic the oxygen by-passed the nebulizer in the expiratory phase of respiration and no appreciable penicillin was lost through the top carburetor opening of the nebulizer. The penicillin aerosol in this technic was thus formed only on inspiration and did not require the co-operation of the patient.

The nebulizer may be suspended or attached to a clysis stand for patients too sick to hold it themselves. We have found, however, that the majority of patients can comfortably hold the apparatus during the 15 or 20 minutes of treatment. For patients who are unable to use the technic described above, the O. E. M. mask may be employed. The nebulizer can be introduced into the face piece of the mask, and the oxygen entrance closed off. Infants and small children can best be treated in enclosed plastocel hoods or in specifically constructed closed chambers, the basic nebulizer and oxygen flows described above being used.

Barach and his associates devised an apparatus for introduction of penicillin aerosol into the nasal accessory sinuses following suction.

We employed this apparatus in a series of 24 patients with infective sinus disease and found it extremely efficient

Prigal and Speer recently described a method of aerosolizing penicillin by the use of steam in place of oxygen flows. This procedure may be of value in infants and children with infective croup, and the aerosol can be directed into the oxygen tent if humidification is particularly desirable

Penicillin Blood Levels Absorption of penicillin from the pulmonary tree into the blood stream was demonstrated by effective penicillin blood levels which ranged from 0.015 to 0.225 units per cc. Peak levels, which were observed at the end of 30 minutes, in some cases persisted for as long as 2 hours. The absorption of penicillin into the blood stream is not necessarily a measure of topical effectiveness of penicillin aerosol. In most of the cases the determination of blood levels is more of academic interest than of practical value. The clinical course is sufficient proof of the topical effectiveness of penicillin aerosol.

Pneumonia Observations in this group of patients definitely proved the efficacy of penicillin aerosol in combating bacterial pneumonia and may serve as the rationale for its subsequent use in suppurative pulmonary disease. Clinical cures were obtained in 9 patients with pneumococcal pneumonia and in 1 with an acute pulmonary infarct and pneumonitis. For the management of pneumonia due to streptococcal, staphylococcal and penicillin-susceptible strains of Friedlander's bacillus, penicillin aerosol therapy is probably more effective than parenteral therapy alone. Combined aerosol and intramuscular therapy may be employed in patients who are seriously ill, particularly those with septicemia. For patients with staphylococcal pneumonia the therapy should be continued for at least a week after all the clinical and roentgenographic signs of infection have subsided.

To control pneumonia due to penicillin-susceptible strains of Friedlander's bacillus we have employed massive doses of 100,000 units at three-hour intervals in 2 cases. In both cases the organisms rapidly disappeared, remaining absent in one case during the course of therapy, in the other, however, the organisms recurred although the patient remained symptom-free for some time after the discontinuance of therapy. The patients with pneumococcal pneumonia required treatment for 3 to 7 days. All were cured, with no ensuing complications, and they were generally discharged between the 6th and the 8th day after hospitalization.

Infective Bronchial Asthma A course of penicillin aerosol lasting from 3 days to 3 weeks was given to 22 patients with severe chronic infective bronchial asthma. The penicillin-susceptible organism promptly disappeared and in most cases remained absent during hospitalization. This therapy was generally disappointing, although striking improvement was occasionally observed. In these patients control of the primary bronchial infection with intramuscular penicillin and oral sulfonamides has proved equally disappointing. Most of the patients observed, however, that they were able to raise sputum more easily while receiving penicillin aerosol. Many objected to the taste and the irritating qualities of the aerosol. The danger of local or generalized allergic reaction to penicillin aerosol in asthmatic patients

must always be kept in mind. Most of the local and urticarial reactions observed occurred in patients with bronchial asthma or bronchiectasis.

Bronchiectasis A series of 80 patients with chronic bronchiectasis were treated with penicillin aerosol. Most of these patients received an initial course of therapy of at least six weeks and subsequently returned for an additional 7 to 10 days of therapy at intervals of 3 to 6 months. Postural drainage was carried out immediately before each treatment. Several of these patients continued to take penicillin aerosol therapy once daily at home throughout this period, this procedure was effective in preparing the patient for surgery and in preventing post-operative infections. Defervescence, lessening of toxicity, diminution in the amount of daily sputum, loss of its foul character, rapid disappearance of the penicillin-susceptible organisms, improvement in the patient's appetite and gain in the weight were uniformly observed. We are ever mindful, of course, that the anatomic changes accompanying bronchiectasis are permanent and cannot be altered by any type of therapy except resection. However, these patients are subject to repeated episodes of infection, pneumonitis or involvement of other lobes. Infection can be eradicated or eliminated by penicillin aerosol, which thus provides the ideal therapy for pre-operative and post-operative cases.

Our experience with streptomycin aerosol has been limited to 2 patients with Friedlander organisms. In our first trial with this drug the streptomycin-susceptible organisms rapidly disappeared when 100,000 units at 8-hour intervals were employed but returned after several days of therapy. We then found it necessary to increase the dose. After a while the organisms became more resistive and could not be eradicated despite tremendous doses. The possible appearance of streptomycin-resistive strains with aerosol should be taken into consideration before such treatment is initiated.

Lung Abscess We have employed penicillin aerosol therapy in a series of 11 patients with lung abscesses. Our observations have impressed us with its value in the aerobic, non-odoriferous, post-pneumonic type of lung abscess, the results with the anaerobic, putrid, atelectatic types were disappointing. Doses of 50,000 units of penicillin given at 8-hour intervals were usually adequate. Postural drainage was generally carried out prior to each treatment. In the more toxic and putrid cases we employed simultaneously 25,000 units of penicillin intramuscularly. Therapy was continued for at least four weeks. With an effective program of penicillin aerosol it is possible to avoid surgery in most of these cases.

Acute Laryngotracheobronchial Edema Six patients with laryngotracheobronchial edema associated with serious infection were treated with penicillin aerosol, constant streams of oxygen or mixtures of 75 per cent helium and 25 per cent oxygen being employed. These patients were moribund at the outset of therapy. The conventional methods of employing sulfonamides, parenteral penicillin and oxygen therapy by catheter, mask and tent had been tried with little benefit. Dramatic improvement was observed as soon as the inhalation program was instituted. It was the opinion of many observers that the recovery of these patients could be directly attributed to the above therapy.

Pulmonary Emphysema and Emphysematous Blebs We have recently observed striking improvement in a series of 6 patients with severe pulmonary emphysema when penicillin aerosol was added to the usual program. We believe that all patients with severe pulmonary emphysema who fail to improve with the usual treatment should receive a course of penicillin aerosol therapy.

Penicillin aerosol therapy should not be employed by the nasal or pulmonary route for the management of the *common cold*. This infection generally runs a self-limited course despite all so-called "useful therapy." One must always bear in mind the possibility of the appearance of penicillin-resistant strains in all cases of repeated or prolonged penicillin aerosol therapy.

SIMPLIFICATION OF PENICILLIN AEROSOL THERAPY FOR HOME TREATMENT by WALTER FINKE, M.D. (*American Practitioner*, Aug 47, Pp 643-644) Prolonged administration of penicillin aerosol has proved a valuable therapeutic measure in bronchopulmonary infections. In order to achieve more than temporary results in subacute and chronic conditions, continuation of this treatment in the patient's home for several weeks and even months is necessary.

In the hospital, compressed air or oxygen is generally used as a nebulizing agent. For use at the patient's home, a hand nebulizer may prove adequate for short treatments. However, for any longer treatment, this cumbersome method requires some endurance in the patient. The time-consuming procedure, and especially the strain on the patient's hand, frequently leads to a relaxation in the correct administration of the antibiotic, and consequently, unsatisfactorily therapeutic effects. Another shortcoming of the current mode of penicillin aerosol therapy is the rather complicated method by which the penicillin must be dissolved in the vial and the required dose taken out for each treatment. Unless carefully done, this procedure makes a certain loss of penicillin unavoidable. Furthermore, to avoid deterioration the remaining penicillin solution must be stored in a refrigerator for succeeding treatments.

For the past two years, this writer has been trying to help his patients continue the treatment at home by inexpensive methods which involve as little inconvenience as is compatible with full therapeutic effect. The best method arrived at makes use of a *simple bicycle or motor pump* and of penicillin triturate tablets.

Two types of inexpensive hand pumps were found most convenient and efficient for patients who were unwilling or financially unable to use oxygen. The one can be attached to a board, thus giving the patient a sufficiently large base to hold the pump with one foot. The other type can be fastened within easy reach of the patient, for example, on the chair which he occupies during treatment. The former furnishes a rather high pressure and is most appropriate for adults. The latter is a little less forceful, but can be handled very easily, even by children. Both are considerably less tiresome and time-consuming than a hand bulb, and, in my opinion, more convenient for the patient than the automobile foot pump suggested by Barach.

In order to prepare the pump for penicillin aerosol administration, *the valve at the end of the rubber hose is cut off*, and pump and nebulizer are connected by means of rubber tubing. To obtain filtered air for aerosolization, a small glass-wool filter can be inserted into the air stream.

The patient holds the nebulizer in one hand, his other hand grasping the pump handle. While inhaling deeply and slowly, he presses the handle down, holds his breath for a few seconds and then empties his lungs through the nose or mouth, withdrawing the handle at the same time. If the larger type pump is used, sufficient pressure is obtained by pressing the plunger only part way down.

Instead of penicillin as furnished in vials, triturate tablets are used. These provide a fresh supply for each treatment without having to be kept cool. One or more tablets, each containing 50,000 units of crystalline G-penicillin, are put into the nebulizer and 1 cc distilled water added. Although even four tablets dissolve easily in this amount of water, it is recommended that for more than two tablets, at least 1.5 cc should be used since highly concentrated solutions occasionally disagree with the patient.

A single treatment of penicillin aerosol following the above outlined method takes from 10 to 15 minutes. This includes the time elapsing before that penicillin which condenses in the nebulizer drops back to the bottom. Although 1 cc solution can be nebulized in a much shorter time, it should be emphasized that for obtaining the best possible results any undue efforts to save a few minutes should be discouraged.

Our Problems a forum for discussion

OBSERVATIONS ON AYURVEDIC AND YUNANI SYSTEMS OF MEDICINE

It appears from the terms of reference to the Chopra Committee that the Government of India accepts the value "indigenous systems" of medicine as scientific systems or rather as equivalents of medical science, and only desires to receive recommendations from the present committee as to how facilities could be provided for training practitioners of these so called 'systems' and how they could be made more generally 'useful' to the public. All scientifically minded men will fundamentally differ on this point. No modern government that can claim to be called "civilised" would ever accept the existence, and far less encourage 'systems' in any Natural Science, including Medicine. There are no systems in Engineering or even in Biology. But there are systems of Philosophy. The medical science of today is no more based on metaphysical speculations as the ancient and medieval medicines in the East and West were. For example, the Western Medicine also consisted of systems in the 17th and especially in the 18th centuries, called the period of systems in the history of Medicine. But the Modern Medicine is not so, and being founded on the Natural Sciences (called the 'fundamental sciences' of Medicine) it, in the words of Claude Bernard,—"believes and accepts everything, provided that it is based on observation and proved by experiment." The systems, on the other hand, are based on tradition and authority. The traditional medicine in the West was called allopathy to distinguish it from other systems, such as Homoeopathy, which were prevalent at that time in

done to prevent malpractices There should not be an uncontrolled exploitation of the public sentiments, in favour of the indigenous systems Government should enforce by laws a sufficient fundamental education in modern sciences, 'pre-medical' (such as Physics, Chemistry, and Biology) and 'medical' (such as Anatomy, Physiology, Pathology, and Pharmacology) of about the same standard as required for the qualification in Modern Medicine There should be no short cut to medical practice *Nobody should be allowed to use modern remedies without having learnt the scientific basis of their use*

Practitioners knowing the fundamental sciences will be useful in the work of preventive medicine, but one cannot say to what extent they will be useful in the work of medical relief without the knowledge of modern clinical sciences A well known French Physician has said "Medicine sometimes cures, it often relieves, it always consoles" So these practitioners also will always console, sometimes relieve but rarely cure!

All interested in our culture and science will agree that a serious, critical and unbiassed study and interpretation of the ayurvedic texts ought to be undertaken by some competent bodies or institutions But the money spent as at present on the training in 'systems' is not only a waste but a definite obstacle to the development of scientific medicine This can better be used to provide facilities to the students of Modern Medicine to get acquainted with the general principles and characteristics of the indigenous systems, before they go out into the public At present doctors who qualify from the medical colleges are quite ignorant of these systems In their after-life, they have to answer all sorts of questions about them from the public Then, they are either carried away by their sentiments, or they find it advantageous to pamper the popular prejudices, or they acquire from hearsay very distorted ideas about the systems, because they have not been taught the difference between science and systems and they do not know through what stages Modern Medicine has passed before it ceased to be a system or a 'pathy' It is, therefore, necessary to give a *historical basis* to the medical education in our colleges with particular reference to the indigenous systems and their relationship to the Greek and Arab Medicines and the relationship of the latter to the ancient Indian Medicine Therefore, every medical college in India must have a department of the History of Medicine Prof Sigerist who had recently visited this country at the invitation of the Government of India has stressed the importance of an Institute of the History of Medicine in India

The students of 'Modern Medicine' should be taught the characteristics of the indigenous systems along with the history of medicine at the end of their course, after they have learnt the principles of modern medicine, or during the period of Internship if such a compulsory period is introduced before registration

There can be only one Medical Science This excludes all systems, and so the question of fusion should not arise The idea is repugnant to the scientific mind On the other hand, useful knowledge that will throw further light on disease and its treatment should be welcome

Since modern medicine is not a system, there is no other 'Western System' at present prevalent in India than Homoeopathy Many

qualified 'doctors' also give homoeopathic treatment. Full medical qualification must be made compulsory even for homeopathic practice. Other 'Western systems' or fads, such as Osteopathy, Christian Science and the so called Naturopathy are not yet fortunately prevalent in this country although the last one is receiving some support from certain political leaders.

The establishment of the Institute or Departments of the History of Medicine in the different existing Medical Colleges will lead to the study and their relations or connections with the old practices of medicine in other countries such as China, Tibet, Persia, Arabia, and even Greece and Egypt. The Ayurvedic theories and remedies can be experimentally tested in the laboratories of the colleges, its methods of diagnosis and treatment can be tried and compared with the present methods in the wards of the associated hospitals. Such work in connection with the Unani System may now be left to the colleges in the Pakistan areas.

Modern Medicine will accept whatever will be so established by the methods of observation and experiment.

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Notes on New Drugs and Preparations

AMOEBINDON

- 1 *Name of Drug* AMOEBINDON (*Indo-Pharma Pharmaceutical Works, Bombay 14*)
- 2 *Composition* Di iodo hydroxyquinoline, 3.2 grains (0.21 grammes) per tablet (64% of Iodine)
- 3 *Dosage* *Acute cases* A minimum of 1 tablet 4 times daily for 15 days, to be repeated, if necessary
Chronic cases A minimum of 6 tablets daily for 20 days
Can be given concurrently with emetine injections in cases of amoebic hepatitis
- 4 *Indications* Amoebic Dysentery, acute and chronic, Balantidial infections, Lambliasis, Colitis, Summer Diarrhoeas
- 5 *Toxic Symptoms* None
- 6 *Packings* Bottles of 30 and 60 tablets. Hospital Packings of 250, 500 and 1,000 tablets

SYNTHETIC PREPARATION OF VITAMIN A

J. F. Arens and D. A. van Dorp of Oss (Holland) have solved the problem of the artificial preparation of vitamin A after four years research. Synthetic preparation of vitamin A which upto now was only available from natural sources, such as, milk butter, yolk, liver, and codliver oil, is of great importance to the medical men and the pharmaceutical and foodstuff industry. Vitamin A deficiencies are fairly common and widespread in India, and its synthetic preparation, if it leads to mass production making it possible to market it cheaply so that even the poorest can avail of it, will confer a great benefit on the suffering humanity. The vegetable oil manufactured in India for human consumption should be reinforced with vitamin A and D either synthetic or natural.

Reflections and Aphorisms

"There is one difficult problem in medicine that awaits solution. Humanity, and living matter generally could not have continued to survive had it not been from the beginning capable by nature of holding its own in the battle with the outer world (including the bacteria). Have the physicians had any influence, in historic times, on this ascent of humanity, or would everything have been the same (for humanity as a whole) had there never been any physicians, but only magicians, quacksalvers and wise-women? The relation of the physician to the patient is something entirely personal, individual, it is something psychological, a faith or superstition, that drives the sufferer to the titled specialist, no less than to the quack or wisewoman, the physician is the product of humanity's need, of its hope for protection, he is a longing, a spiritual postulate. He is the retail dealer in scientific doctrines, the traveller in dogmas and theories. He is supposed to translate the wisdom of the discoverer of general truths into a form which is applicable to individual cases, for the physician must be an individualist, whereas science is bound to generalize.

"But all humanity fights organically and naturally of itself, in itself, and outside itself, against the things that threaten it. Through the generations, by hecatombs of unthinkable sacrifices, it builds within itself organic barriers, it arms itself against noxious influences, it achieves congenital immunities.

"This is a long, long path, leading through wilderness of graves, and in this struggle every dying man is in some degree a Christ, a saviour who dies for his brother, because he helps a little, even by his sacrifice, to reduce the deadliness of some enemy of his posterity. Always humanity has been preceded by a pilgrim chorus of the sacrificed.

"And now comes science, and thinks to shorten this path by hundreds and thousands of years, by the artificial cultivation of the powers of resistance.

"This is the problem. Can it be solved? Can therapeutic skill put its shoulder to the wheel and accelerate the natural, slow, but steady progress of natural self-protection, can we snap our intellectual fingers in the face of death, and with the weapon of an Ehrlich in our hands heal the sick not individually, as now, but quite generally, to some extent in the laboratory, with a blood-test before us, and without ever seeing the patient face to face? This is the problem that confronts us.

"But the physician, who may balk a little at this spectral prospect of an impersonal medicine, holds one thing in his well-tryed, humane, consoling hand which no laboratory, no reaction, no theory of toxams can ever wrest from him and that is the soul of his patient. The more general and universal medicine may become, the more profoundly psychological, the more ethical and cultivated and high-minded must the physician be, the more surely he must hasten to make general the new therapeutic methods, outstripping the monopolies and specialties, in the quiet room where confession and consolation and spiritual mediation do their beneficent work."

CARL LUDWIG SCHLEICH
(Those Were Good Days)

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Original Contributions

THE WORLD OF MEDICINE—ONE WORLD*

by

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Tendencies to revive Ayurvedic medicine and to encourage its application in daily practice are increasing in intensity and are backed by various Provincial and State Governments. Nationalistic feeling and historical sentiment, not limited by any medical judgment, are intermingling in a peculiar way. The supporters of this revival movement are praising medical methods of the past because they were purely Indian and condemning modern scientific medicine because it is foreign, "western". Such a differentiation, based mainly on emotional grounds, faintly reminds of Nazi ideology which banned the use of Salvarsan because it was invented by the Jew, Paul Ehrlich, and omitted the name of Haffkine from German text books of Tropical Medicine because he too was a Jew. However, the assumption of a *contrast* between Indian and Western medicine and that of a self-contained indigenous system should be investigated from a medico-historical point of view, although the present writer can not claim to be more than an amateur historian.

SOURCES OF GREEK MEDICINE

The easiest way of approach to our problem seems to be a scrutiny of the origins of Greek medicine which, beyond doubt, forms the foundation of modern scientific medicine. The Greeks, composed of at least half a dozen Aryan tribes, from the 3rd millennium B C to about 1000 B C, invaded in several waves first the Balkan peninsula, then the Aegean islands and, finally, some of them, the Ionians, Achaeans and Aeolians, settled along the coast of Asia Minor. Throughout this long prehistoric period of successive migrations on the peninsula as well as on the islands, they penetrated into territory occupied by the Karians, an Asiatic people of old civilization and highly developed craftsmanship, worshipping a great female deity and, accordingly, living in a social system of matriarchate (mother's rule), such as is still in force in Cochin and Travancore. It is more than probable that the Karians, in times unknown, had come the same way as the Greeks but in the opposite direction, from Asia Minor to the islands and from there to the peninsula. Gradually, the barbarian Greek conquerors assimilated the culture of the indigenous population and some elements of other surrounding civilizations too.

* Inaugural Lecture Medical College Union, Jaipur, December 6, 1947

Greek art of the 9th and 8th century B C, especially that of the islands and of Asia Minor, clearly shows how deeply influenced they were by the Middle East and by Egypt. And what is true of early Greek sculpture is also clearly expressed by the life history of the earliest Greek (Ionian) natural philosopher, *Thales of Milet* (ca 600-500 B C), a wealthy merchant, whose earlier years were spent in travelling. From Egypt he brought geometrical experience which enabled him to estimate the distance of ships at sea, from Babylonia such profound astronomical knowledge, that he exactly predicted an eclipse in 585 B C, and from the Phoenicians the secret of navigation according to the stars. If the founder of Greek philosophy was so strongly influenced by the wisdom of the Orient, if early Greek art represents a synthesis of oriental and nomadic-aryan elements, is it thinkable that Greek medicine alone should have remained unaware of the cultural atmosphere in which it developed?

To answer this question and to come to a solution of our central problem, whether medicine in Europe developed independently of the East or in close correlation with it, we have to look at the condition of medicine in those areas with which Greece was in contact before her own medicine culminated in *Hippocrates* (460-370 B C), often and wrongly called the 'Father of Medicine'. The travels of Thales and still more those of the great historian Herodotus, (425 B C) clearly indicate that the roots of Greek philosophy and science are to be found in Egypt and Mesopotamia.

EGYPT

Until recently, historians were surprised by the scarcity and poor quality of medical documents, found in Egypt, compared with the greatness of her art and architecture. This certainly is due to the fact that medical papyri existed only in a few copies, the art of healing, derived from Imhotep (ca 2850 B C), having been a jealously guarded prerogative of the temples, there the sacred Hermetic books of the god Thoth, of which six were devoted to medicine, have been kept and the existing papyri are supposed to be remnants of those lost compendia. The two most important papyri, both written at about 1500 B C, are apparently copies of much older originals (ca 1800 B C). The one, called after its collector Edwin Smith, is a fragment of a textbook of the treatment of fractures, luxations, wounds and bruises, it treats the subject according to the affected region from the head downwards, unfortunately the preserved part of the text ends with the chest. Surgical instruments and the use of splints are mentioned. Wounds were dressed initially with fresh flesh, later with fat and honey. The other papyrus, called Ebers after its discoverer, is a kind of materia medica and a textbook of medical treatment, it is complete and contains 900 different prescriptions, accompanied by the texts of all the charms and mantras which have to be chanted while using the remedies, among which are bile and fat of various animals. In addition, it reveals some of the prevailing physiological ideas, such as that the heart is the principal vital organ and the ears organs of hearing as well as of respiration. Of minor papyri, one called Kahun, written in about 1850 B C deals with gynaecology, another one of 1450 B C (kept in Berlin) represents the oldest known work on pediatrics. Although in the days of the awakening of intellectual interests in Greece, Egypt had lost much of

its political and cultural hegemony, Herodotus proves that it still was a most impressive emporium of civilization, studied by Greek philosophers and scientists with deep devotion and admiration.

MESOPOTAMIA

In Mesopotamia flourished the highly developed civilization of the Sumerians before 4000 B C (Woolley, 1929), its craftsmanship in the artistic use of precious metals and stones remained unsurpassed. About the life of their successors, the people of Sumer and Akkad, we are surprisingly well informed through the Code of Laws of King Hammurabi (ca. 1950 B C) which is of special interest to us. There we find (laws 215 to 225) the oldest regulations of medical fees for successful operations but also of punishments meted out to surgeons for destruction of an eye or the fatal issue of an operation in general, the punishment depends on the seriousness of the afflicted damage and on the social status of the patient, whether he was a slave or a freeman. Even veterinary fees and compensations for loss of animals due to medical interference are fixed. This certainly proves the existence of a medical profession of old standing in Mesopotamia, 4000 years ago.

INDIA

The Sumerians were in trade relationship with the oldest civilization known on Indian soil, the pre-Aryan Indus valley culture, which flourished in the 3rd millennium B C and was destroyed by the Aryan invaders who reached this peninsula at about 2000 B C, at the same time as their brethren entered the twilight of Greek prehistory on the Balkan peninsula. These barbarians are obviously responsible for the fact that the only means left for estimating the standard of medical knowledge in those days are the public health institutions of the cities, best preserved in Mohendjodaro. There, the public and private bathing arrangements, the town sanitation by perfect sewer systems and the town planning as a whole are of a standard which was never again reached in India on such a tremendous scale and remained unknown in Europe until late in the 19th century. It is impossible to imagine that such a triumph of public and individual hygiene could have been achieved without a medical science, progressed far beyond anything achieved at the same time anywhere else. Sumerian seals found in Mohendjodaro prove the existence of trade connections between Mesopotamia and India, it seems probable enough that medical knowledge too travelled along these routes in both directions. The Aryan invasion certainly put the clock back by several centuries and prevented progress for a long time. But, as far as medicine is concerned, the gap in historical records of some 15 centuries, from the sack of Mohendjodaro and Harappa to the days of Buddha, is bridged by historical conjecture. Apart from occasional medical hints in the Rigveda, the oldest Indian text devoted to medicine was the Ayurveda, which formed part of the Atharvaveda, conservatively dated at about 1500 B C. Susruta enumerates its eight parts. The proper chronology of Susruta, the great surgeon, is of crucial importance. It is most probable that the Susruta Samhitā was finally edited after Charaka, who was identified as Court physician to King Kanishka (78-101 A D), as its present text shows definite improvements over the Atreya-Charaka Samhitā. Susruta's systematic arrangement of his material is perfect and com-

parable to any occidental textbook. He shows more differentiation and greater exactitude than Charaka when both are dealing with the same subject, so, for instance, he describes five different sizes of the tube to be introduced into anal fistulas, while Charaka used only three and he gives their exact measurements whereas Charaka compares them with the size of various fruits. On the other hand, the famous Bower manuscript of the 4th or 5th century A.D. quotes Susruta as a classic authority, closest study of this manuscript, written on 51 birch bark leaves, induced Hoernle, an almost infallible expert of Indology, to place the original Susruta in the 6th century B.C. as a younger contemporary of the oldest Indian Physician, Atreya. Such a timing also fits the fact that Vagbhata who lived about 625 A.D. and is the third of the "Vṛiddha Trayī" comments on both his great predecessors, Susruta and Charaka, as belonging to the distant past.

Without being able to read the original texts, drawing my conclusions from the medico-historical literature at my disposal, I think that the beginnings of the Susruta Samhitā, although not in its present form, reach back to the 6th or 5th century B.C., almost to the same time as those of the Atreya-Charaka Samhitā. Certainly, there remains room for conjecture as everywhere in early Indian chronology. But what we want to prove is that Indian medicine of the 5th century B.C. was on such a high level that the Greeks could be influenced by it and incorporated its essence into the body of their system and in their teaching, and not, or not mainly, the other way round. The similarities between the concepts of the physiology of digestion, of metabolism and circulation, as they are expounded by Susruta and in Aristotle's (384-322 B.C.) "*De Partibus Animalium*," is so striking, sometimes almost literally identical, that an independent parallel development is almost impossible (cf. Kutumbiah, 1939). The question is only, who was earlier, who influenced whom. Nobody doubts that Atreya preceded Hippocrates by more than one century and in all probability the same is true of the earliest author of Susruta's Samhitā. It is certain that Hippocrates used several Indian medicinal drugs (Hemmeter, 1936). Indian surgery reached very early a perfection which the Greeks never even approached, protheses were used in Vedic times. Cataract operation was probably invented in India and complicated abdominal surgery, such as Caesarean section as well as rhinoplasty originated here. Alexander the Great, pupil of Aristotle, according to Nearchos, had his soldiers treated by Indian physicians for snake bite and also for other diseases in which his Greek physicians were less experienced.

Looking at Greek philosophy, we find overwhelming proof of the direction, in which the stream of ideas moved in the 6th century B.C. Pythagoras left Samos, threatened by Persian conquest, in 530 B.C. and founded his school of religious philosophy in southern Italy. His teaching was based on the immortality of the soul and on its *transmigration* (metempsychosis), where else but in India originated this idea? Parmenides, Pythagoras' younger contemporary, warned against "making an instrument of the blind eye, the echoing ear, and the tongue," as enquiries, based on observation by the physical senses would never reveal the truth. "For him change, motion, variety, were all *illusions of the senses*" (Farrington, 1944). Does this not sound

like a quotation from the *Upanishads* ? Plato (428-347 B.C.), a younger contemporary of Hippocrates, had absorbed Indian philosophy so completely that his programmatic work, "*The Republic*" cannot be fully understood without interpretation in terms of Indian thought (Urwick).

These few considerations, which could be multiplied, make it more than probable that the many similarities between Greek and Indian thoughts in medicine as well as in philosophy are due to the fact that the Greeks drew much of their knowledge and way of reasoning from the Hindus (Hammet, 1929) and that we are justified in stating that Greek medicine as handed down to posterity in the *Corpus Hippocraticum* and by Aristotle is a synthesis of East and West, so that in "Western" medicine, which beyond doubt is based on Greek work, earliest Indian achievements are incorporated.

GREEK MEDICINE

However, there is no doubt that the Hippocratic writings in their totality, products of many writers and various ages, represent a stupendous achievement of bio-physiological thinking and closest, well trained observation at the bedside. They formed not only the foundation but a considerable part of medical teaching for the next 2,000 years, an immortality which they share among medical works only with the *Samhitās* of Sūsruta and Atreya-Charaka, and the *Qanun* of Avicenna.

It is impossible to do justice in a few lines to the diversity and profundity of the Hippocratic writings which, perhaps, represent the whole library of the famous medical centre on the island of Cos. In the "*Law*" (*nomos*) the social and moral position of the art of healing as well as the ethical duties of its adepts are defined on a standard, beyond which further improvement is hardly possible, embodied in the Hippocratic Oath, they are still binding on every medical graduate of continental universities. In the book on "*Ancient Medicine*" we find a most remarkable discussion on the importance of food, not only in the sense of diet for the sick, but also on the development of the art of cooking which distinguishes civilized man from the savage. In a deeply impressive way are those rebuked who, like Empedocles, tried to force medical science and treatment to conform to philosophical ideas, applicable only to subjects, which, like cosmology, are unfit for direct observation and investigation. Nevertheless, in the "*Aphorisms*," which were used as a text book up to the beginning of the 19th century, the famous maxim is laid down that a physician, who knows how to integrate philosophy in medicine, resembles a God. Directions for the behaviour of the medical man under various circumstances and precious advice on bed-side manners are to be found in "*the Physician*". In "*Airs, Waters and Places*" the physician is enjoined to consider climatic conditions, the condition of the soil, the water supply, habits of the people and many other local factors, as they are essential for prognosis and treatment. His "*Prognostic*" is a treasure house of experience even to day. His drugs were simple, he made frequently use of honey and barley, of light diet and enemas, and for the rest he trusted the natural resistance, for "*our natures are the physicians of our diseases*". A short note book, entitled "*In the Surgery*," mentions wound treatment with tar and recommends to practice all operations with both hands. His anatomy is rather primitive. Physiology and

pathology are based on the doctrine of the four humours and show great similarity with the Hindu concept of the tri-dhatu, elaborated further by the correlation of the seven dhatus,—rasa, blood, flesh, fat, bone, marrow and semen

Hippocratic medicine, incorporating the fruits of previous and contemporary medical achievements, showed hardly any further development in Greece proper, which some thirty years after Hippocrates' death lost its political independence to the Macedonians whose king Philip defeated them at Chaeronea in 346 B C

During those critical years *Aristotle* (384-322 B C), the sage of Stagira in Thracia, and one of the greatest biologists of all times, achieved a unique task of singular importance for generations to come. Not content with carrying out research on the most diverse subjects like embryology and the life of the bees, he put into a perfect system all the knowledge of all the sciences and all the thought of philosophers, accumulated up to his time. His work became and remained for 1,800 years guide and measure of all scientific and philosophic endeavour. Alexandria, the Arabic world and the Christian Church recognized him as the highest authority and deep into the revolution of the European Renaissance his word was the last, inappellable judgment. Even India might have felt the repercussions of this giant encyclopaedist. An essential part of his work is devoted to medicine, although he never practised it, clarifying and codifying Hippocratic teaching and improving upon the four humour doctrine, which corresponded to the four elements, by the introduction of a fifth one, the all pervading pneuma, comparable to the Indian fifth element, *ākāśa*. For the historian, Aristotle's writings are of the greatest interest because dates and facts of his life are well documented and permit an exact determination of the time, at which the ideas incorporated in his work were known.

ALEXANDRIA

Philip's son Alexander the Great, one of the few men who changed the face of the world, widened the Greek sphere of influence so that the Greek way of living and thinking remained a permanent force wherever civilization existed for the following 2,000 years. Apart from many other cities, he founded Alexandria in Egypt and his genius made it the centre of every kind of scientific life upto 641 A D, that is for one millennium. There, in about 300 B C, Herophilus and Erasistratos laid the lasting foundations of anatomy and physiology, there, fifty years later, Euclid determined the development of geometry and mathematics up to our days.

ROME

In Alexandria were trained all those Greeks who brought scientific medicine to Rome where, due to social prejudice, an indigenous system of medicine never existed. We have only to look at the names of the leading medical men in Rome, the empiricist *Ashlepiades* of Bithynia in the first century B C, *Soranus* of Ephesos, the founder of gynaecology and midwifery, and his younger contemporary, *Galenos* of Pergamon (+204), both in the 2nd century A D, all of them were Greeks. The only Roman who achieved importance in medical history, *Celsus* (1st half, 1st century A D), was not a medical man at all.

(To be continued)

ACUTE CORONARY OCCLUSION

A STUDY OF 82 CASES WITH SPECIAL REFERENCE TO SOME LESS KNOWN FACTS

by

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(Continued from page 17)

Shock Though shock is a prominent outcome of coronary occlusion at times it can also be the cause of coronary occlusion. From an analysis of 350 cases of coronary occlusion Blugmgart³³ and his co-workers found multiple fresh coronary occlusions in 11 instances which occurred while the patients were in a state of shock variously produced by such diverse conditions like pneumonia, massive haematemesis, diabetic coma, pulmonary infarction, congestive cardiac failure and uraemia. In addition they describe 38 cases where single fresh occlusion was found as a result of shock, approximately 50 per cent of them being shock of non-cardiac origin.

Relationship to Angina It has been observed that angina pectoris may precede, be associated with or follow an episode of coronary occlusion. 41.66 per cent of the 108 patients reported by Fisher and Zukermann²⁴ had history of anginal attacks prior to their attacks of coronary occlusion. Smith Sauls and Ballew²¹ report 46 per cent as having previous angina and in this study 14 patients (17 per cent) had angina prior to their coronary occlusion. It is not uncommon for angina to appear for the first time after an episode of coronary occlusion and Smith Sauls and Ballew²¹ as well as Cassidy⁸ found the incidence of post-coronary angina in about 23 per cent of their cases, whereas 33 per cent of the cases of these authors had angina both before and after coronary occlusion. As many as 13 per cent of their patients found that their angina was relieved after the coronary occlusion, probably due to complete obliteration of the sclerotic vessel which was responsible for the angina.

The incidence of various factors which could have any possible bearing on the aetiology of coronary occlusion in this study have been summarised in table No. 8.

TABLE 8 Aetiological factors

| Factors | No. of cases | Factor | No. of cases |
|------------------|--------------|----------------------|--------------|
| Hypertension | 33 | Anaemia | 4 |
| Angina | 14 | Mental stress | 4 |
| Arteriosclerosis | 13 | Diabetes | 3 |
| Obesity | 11 | Acute infect. fevers | 3 |
| Tobacco | 11 | Rheumatic infection | 1 |
| Physical stress | 9 | Cholecystitis | Nil |
| Alcohol (excess) | 8 | Shock | Nil |
| Syphilis | 6 | Trauma | Nil |

Mode of onset The usual time of onset of the attack is in the early hours of the morning between 2 and 4 a.m., the time at which

cardiac asthma is most frequently experienced. However, the mode of onset in the younger age groups does not follow the set rule. In their series of 80 American servicemen, French and Dock¹³ found that only 3 died during sleep, 14 had the attack within 2 hours of getting up in the morning, 15 during severe physical exertion, 26 within a few hours of exertion and 8 while straining at stool, probably the dangerous Valsalva effect. In the series here reported a study of the time and mode of onset could be made in 53 cases only, 10 of them developing the attack during sleep. The details are shown in Table 9.

TABLE 9 Mode of onset

| Mode of onset | During sleep | While resting | During routine work | After food | During or immediately after stress | Combination of any of the preceding | Total |
|---------------|--------------|---------------|---------------------|------------|------------------------------------|-------------------------------------|-------|
| No. of cases | 10 | 21 | 7 | 3 | 9 | 3 | 53 |
| Percentage | 18.9 | 39.6 | 13.2 | 5.7 | 16.9 | 5.7 | 100 |

One of these cases developed the attack of acute coronary occlusion immediately after intravenous administration of 0.25 gm. of thioethylamine ethylene diamine diluted with 25 cc. of 25 per cent glucose solution.

Seasonal incidence It is generally believed that lower temperature excites coronary spasm and facilitates the onset of occlusion. There are no definite figures to support this statement, though angina pectoris is definitely shown to be precipitated by lower temperatures. In the series here presented the incidence of coronary occlusion during the warmer months and that during the colder months does not show a significant difference except during the years of 1944 and 1945. Probably the difference between the summer and the winter temperatures in Bombay is not sufficiently marked to make any appreciable differences. The details are shown in Table 10.

TABLE 10 Seasonal incidence

| Year | 1941 | 1942 | 1943 | 1944 | 1945 | Total |
|------------------------|------|------|------|------|------|-------|
| No. of cases in summer | 0 | 5 | 9 | 3 | 12 | 38 |
| No. of cases in winter | 5 | 0 | 8 | 10 | 18 | 41 |

Pathology Limitations of time do not permit a detailed discussion of the very interesting studies in pathology of acute coronary occlusion but the mention of a few important facts will help in understanding what, at the first sight, appear to be the vagaries in the symptomatology of the disease. For coronary occlusion to occur in absence of an embolus, it is absolutely essential that the coronary arteries should be damaged. It should be appreciated that coronary sclerosis can occur in young adults or even before adolescence as shown by the work of Master³⁴ and his colleagues and that rheumatic infection can produce similar changes in the coronary arteries as shown by Karsner and

Bayliss²⁸ Vascular spasm may at times be an additional factor. The symptoms produced by the occlusion of a coronary artery depend entirely upon the condition of collateral circulation existing at the time of occlusion of a particular branch (For a better understanding of coronary circulation the work of Schlesinger^{25 26} is recommended to those who are interested) If the branch occluded is a small one or if the anastomotic channels have been adequately developed, not only will the clinical signs and symptoms be absent or misleading but also repeated electro-cardiographic studies may fail to show the classical pattern of myocardial infarction or may only show evanescent changes in the normal pattern or such changes may only be shown after an anoxaemia test (Levy and his colleagues³⁷) or after the standard two step exercise advocated by Master and his Mt Sinai band³⁸

The left coronary artery is more often blocked than the right. The figures of various authors are compared in Table 11

TABLE 11 Site of occlusion

| Author | Apple- sum 30 and Nicholson | Fisher 24 and Zukermann | Lrench 13 and Dock | 14 Newmann | 1 present series | Total |
|--------------|-----------------------------------|-------------------------------|--------------------------|---------------|---------------------|-------|
| Left | 126 | 64 | 63 | 17 | 30 | 300 |
| Right | 42 | 33 | 11 | 0 | 26 | 112 |
| Both | | | 6 | 10 | | 22 |
| Undetermined | | 11 | | | 32 | 43 |
| Total | 168 | 108 | 80 | 30 | 82 | 477 |

It will be seen from this table that of a total of 477 cases the left coronary artery has been occluded in as many as 300 cases (63 per cent.)

Symptoms and Signs *Prodromata* An acute attack of coronary occlusion may fall as a bolt from the blue or may be preceded by vague or definite promonitory symptoms. Holzer and Polzer¹⁶ state that all of their 51 cases had prodromal symptoms, almost always a sensation of precordial pressure of varying strength, during physical exertion or mental excitement. 10 of Newmann's¹⁴ cases reported chest pains before their attacks and in each of these, coronary disease was ruled out after a careful study. 1 of his cases had dyspnoea of unexplained origin, while 3 more complained of palpitations before their attacks—25 per cent of Prof Hume's cases (quoted by Cassidy⁸) had premonitory symptoms. Blumenthal and Reisinger⁴⁰ consider that the prodromal pain may be due to intramural haemorrhage, though the definite mechanism is not known. In the present series 10 of the 82 cases had prodromal pain within 48 hours prior to the attack.

The attack itself in its classical form consists of substernal pain with or without radiation and associated with restlessness, dyspnoea, angor animi, excessive sweating, cold and clammy skin, fast and feeble pulse and a fall in the blood pressure. These may be associated with nausea, vomiting, flatulance, diarrhoea, hiccough, haemoptysis, signs of pulmonary congestion or pulmonary oedema, disturbances of cardiac rhythm, increase in size of the heart, acute cardiac failure etc., and later on there may appear a rise in the temperature and a pericardial friction rub. It must however be remembered that one or more or all of these signs may not be present. 50 per cent of Prof Hume's

(Cassidy⁸) 60 fatal cases of coronary occlusions were found to have evidence of previous attacks at necropsy but barring a single isolated instance there was no clinical history of the episode in them, showing that these attacks were symptomless French and Dock¹³ report a case who had at autopsy an infarction of the myocardium a few weeks old, but had had no symptoms whatsoever in spite of active military life till he dropped down with a haemiplegia of embolic origin 4 days prior to his death The embolus was from a mural thrombus Fisher and Zukermann²⁴ report 10 asymptomatic cases in their series of 108 In the present series, which has been collected from a therapeutic centre, there is not a single symptomless case for obvious reasons

Pain Though a substernal pain of varying intensity is a cardinal symptom of coronary occlusion it need not always be present In the series, here presented, as many as 76 cases (92.7 per cent) had pain of a varying intensity whereas 6 cases had no pain though they had other symptoms The classical description of coronary pain and its vagaries are too well known to require repetition here The findings in the present series are summarised in Table 12

TABLE 12: Pain (76 cases)

| | Intensity | | | | Situation | | | |
|----------------------|--------------|----------|------|--------|----------------|------------|-----------|-----------|
| | Severe | Moderate | Mild | Absent | Substernal | Precordial | Abdominal | Elsewhere |
| No. of cases | 69 | 11 | 6 | 0 | 57 | 9 | 6 | 4 |
| Incidence Percentage | 70.9% | 14.5% | 7.8% | 7.8% | 75.1% | 11.8% | 7.9% | 5.2% |
| | Radiation 70 | | | | No radiation 6 | | | |

Of the 4 cases where pain is recorded to be elsewhere one had pain in the neck, one in interscapular region, one in the left side of chest over the splenic area, and one had pain simulating a renal colic 65 of the seventy cases that had radiation of pain complained of the pain in the left shoulder or the left upper extremity In one the pain was radiated to the right shoulder joint and along the right arm and in four others the pain was radiating down the back along the left 10th intercostal nerve, along the ureter and to the basi-occiput from their respective abnormal situations Angor animi was found in 36 (43.9 per cent), symptoms of shock in 53 (64.6 per cent), dyspnoea in 39 (47.6 per cent), vomiting in 31 (37.8 per cent) and a rise of temperature in 27 (32.9 per cent) of the 82 cases The incidence of various symptoms is summarised in Table 13

TABLE 13 Symptoms

| Symptoms | No. of cases | Incidence Percentage |
|----------------------|--------------|----------------------|
| Pain | 76 | 92.7 |
| Shock | 53 | 64.6 |
| Dyspnoea | 39 | 47.6 |
| Angor Animæ | 36 | 43.9 |
| Vomitting | 31 | 37.8 |
| Fever | 27 | 32.9 |
| Nausea | 11 | 13.5 |
| Flatulence | 11 | 13.5 |
| Hiccough | 4 | 4.8 |
| Evacuation of bowels | 4 | 4.8 |

Though it is true that the triad of pain, collapse and dyspnoea is often present and suggestive of the diagnosis in a fair number of cases, there are others where these symptoms may be absent, and others may be present, which may not point to the heart as the seat of lesion. Cases of coronary occlusion may be mistaken for nervous or cerebral lesions when the presenting signs are a mere feeling of weakness, vertigo, monoplegia, hemiplegia, or physical disturbances from cerebral anaemia, thrombosis or embolism as in 13 cases reported by Stroud and Wagner⁴¹. Reviewing a series of 875 cases of coronary occlusion Pollard and Harwill⁴² came across 17 such atypical cases. In the present series 2 cases were admitted to the surgical wards, one for renal colic and the other for peritonitis. One case was investigated in the medical wards for a left cervical rib before the heart condition was thought of, and the morning cough and dyspnoea of sudden onset in an apparently healthy young individual with a blood pressure within normal limits lead to a probable diagnosis of tropical eosinophilia before the cardiac lesion was detected.

Signs A fall in the blood pressure, tachycardia or unusually a bradycardia with or without alteration in cardiac rhythm, a change in the quality of the heart sounds, evidences of pulmonary congestion and left sided cardiac failure or congestive failure, pericardial friction rub, rise of temperature and an increase in the size of heart may be found associated with the symptoms previously described in a case of acute coronary occlusion.

Blood pressure A fall in the blood pressure is noted in almost every case of coronary occlusion and forms a cardinal sign of the clinical picture. Its importance in the differentiation of cases of angina from those of coronary occlusion was recognised as early as 1915 by Sir Clifford Albutt⁴³. The fall in the pressure may however not be immediate in every case, occasionally in cases of severe pain there may be an initial, though transitory, rise of the systolic pressure. The fall in pressure may be rapid *i.e.* within 3 days (57 per cent) or gradual, *i.e.* taking 7 to 21 days to reach the lowest level (42.5 per cent). In the course of a study of 538 cases Master²⁵ and his colleagues found that a precipitate fall was found only in 9 per cent (100 mm systolic on the 1st day) and a level of systolic pressure of 100 mm systolic or below was attained in 34 per cent. In 18 per cent the pressure remained at that level at the time of discharge. They came to the conclusion that the fall is more rapid in non hypertensives. The mechanism of this initial fall in systolic pressure is not fully understood. So far it was attributed to peripheral circulatory failure reflexly produced from the heart and secondary reduction of cardiac output. Recently however the concept of primary cardiogenic shock has been evolved. This postulates a primary diminution of cardiac output as a result of damaged myocardium. This factor certainly is responsible for the pressure maintaining the low level a few days after the attack but whether it comes into play immediately and causes the initial fall, is not certain. In the series here presented a drop in pressure was recorded in all the cases except 3 where the pressure, especially the pulse pressure were low at the first reading after admission. These three cases do not show a significant change in the pressure readings throughout their hospital stay. In the six cases, which expired almost immediately, blood pressure could not be recorded. Of the 40 patients who were discharged

as relieved and whose blood pressure have been serially recorded only 10 showed a partial recovery after reaching the lowest level. One of them had a pressure record of 200/180 at the time of his discharge 5 weeks after the attack.

Pericarditis Of the 30 cases who were definitely known to have an anterior infarct 4 developed pericardial friction rub, three of them between the 3rd and 5th day and one between the seventh and the tenth day. Woods and Barnes⁴⁹ reported clinically detectable pericarditis in 5.5 per cent of their 128 patients.

Pulmonary congestion In almost every case of coronary occlusion there is left ventricular inefficiency. This may be obvious as seen by physical signs of pulmonary congestion or at times even of pulmonary oedema. In other cases there may not be any clinical evidence and the congestion may only be detected on a radiological examination. Massie and Miller⁵⁰ studied 16 cases by repeated radiological examination and found the evidence of pulmonary congestion in 12. Clinically only 7 of these 12 had any physical signs. The congestion is maximum during the first week. Selzer⁵¹ estimated the arm to tongue circulation time as an index of left ventricular efficiency in 45 patients and found it to be prolonged in all but three of them. Even in these 3 it was at the maximum normal limit. In the present series as many as 50 cases showed clinical evidences of pulmonary congestion.

Size of the heart It was difficult to estimate the incidence of acute increase in the transverse diameter of the heart, because a number of cases who were subjects of hypertension would probably have had enlargement of the heart prior to their attacks. However, 10 cases in this study showed a clinically detectable increase in the transverse diameter of the heart while under observation. Unfortunately radiological measurements by serial radiograms could not be studied due to shortage of material. However Massie and Miller⁵⁰ who undertook such a study in 16 cases utilising 113 radiograms found that they could not draw any conclusion of value.

Rate and rhythm of the heart A large majority of cases of acute coronary occlusion have tachycardia but persistent bradycardia may occur, particularly in occlusion of the right coronary artery. Holzer and Polzer¹⁶ record a temporary slowing of the pulse in 15 of their 51 cases, the bradycardia in some cases being associated with an auriculo-ventricular block, nodal rhythm or sinus arrhythmia. Stokes-Adam's syndrome and convulsions may result from complete heart-block in case of infarction of the interventricular septum. Convulsions may also result from ventricular fibrillation starting in an irritated segment of ventricular musculature. In the present series one case had such terminal convulsions. Extrasystoles were the commonest disorder of cardiac rhythm in the series under review, being recorded in 31 cases. Embryocardia was recorded in 3 cases and gallop rhythm and auricular fibrillation each in 2 cases.

Congestive cardiac failure This may result either soon after or a few weeks after the attack. In the series here presented 9 of the 82 cases developed congestive cardiac failure, 4 during the first week, two during the second week and one each during the third and fourth and sixth weeks. The various physical signs observed in this series have been summarised in Table 14.

TABLE 14 Signs

| Sign | No of cases | Incidence Percentage |
|------------------------|-------------|----------------------|
| Fall in B P | 73/0/3 | 100 0 |
| Pulmonary cong | 50 | 61 0 |
| Disorder of rhythm | 38 | 40 4 |
| Extrasystoles | 31 | 37 8 |
| Tic-tac rhythm | 3 | 3 7 |
| Gallop rhythm | 2 | 2 4 |
| Auricular fibrillation | 2 | 2 4 |
| Cardiac enlargement | 10 | 12 2 |
| Cong cardiac failure | 0 | 11 0 |
| Pericarditis | 4 | 4 0 |

Diagnosis In a typical case the diagnosis is fairly obvious but all cases are not typical, as mentioned before, and a considerable difficulty may be experienced in arriving at a correct diagnosis and in such cases the electrocardiographic evidences are absolutely essential. The main thing is to suspect a coronary lesion in any case of unexplained discomfort or pain in the chest or any other site where coronary pain could occur and which cannot be definitely accounted for. Similarly unexplained breathlessness and a suspected acute abdomen in an individual with arteriosclerosis should always be put through an electrocardiographic test. With our present state of knowledge as many as 95 per cent of cases of coronary occlusion can be correctly diagnosed with the aid of an electrocardiogram. Our attention was first drawn to the E C G changes after acute coronary occlusion by Dr Fred M. Smith of the Presbyterian Hospital, Chicago, who ligatured the coronary arteries of dogs and studied the E C G changes with Dr James B. Herrick, his colleague on the staff. The diagnosis of acute coronary occlusion was electrocardiographically confirmed for the first time on the 3rd May 1917 in a 37 year old physician who was an ex-internee of the Presbyterian Hospital⁵². The precordial lead introduced by Wolferth and Wood⁵³ in 1932 increased the frequency of E C G diagnosis of coronary occlusion by pointing out the change in the E C G pattern where the standard limb leads failed to show any abnormality. The most definite and characteristic changes of acute coronary occlusion are a deep Q wave and an elevation of R/S-T segment, progressively going in a T-wave inversion in leads I and IV in the anterior infarction or left coronary occlusion and in leads II and III in posterior infarction or the occlusion of the right coronary artery. In case of a single infarct there is usually a reciprocation of the changes in leads I and III. In coronary insufficiency there is R/S-T depression and T-Wave inversion progressing or retrogressing under observation. The deep Q waves are absent and the elevation of R/S-T segment is not seen. The administration of digitalis or large doses of potassium, salts, pericardial effusion, congenital heart disease, pulmonary embolism, exposures of short wave diathermy to left chest or a high placed diaphragm may all produce E C G patterns which may superficially or genuinely simulate coronary disease. Geiger⁵⁴ reports a case of paroxysmal tachycardia of ventricular origin where an E C G taken immediately after the cessation of paroxysm simulated coronary disease. It

is frequently impossible to make a diagnosis of acute coronary occlusion in the presence of intraventricular conduction disorders of a high degree particularly a pre-existing bundle-branch pattern of type I⁶⁶ because R/S-T-elevation and a deep Q wave may be intrinsic in the bundle-branch block pattern and bear no relation to the acute attack. Dressler⁵⁶ describes such a case where the diagnosis of supervening acute coronary occlusion was made from the R T deviation of a ventricular extrasystole. On the other hand, if with a clinical history suggestive of acute coronary occlusion an E C G shows a bundle-branch block appearing for the first time the diagnosis of coronary occlusion is almost certain. Recently the interpretation of a prominent Q₃ has given rise to some confusion in the diagnosis of myocardial infarction. The criteria of a Q₃ of coronary occlusion (Pardee Q) have been admirably summarised by Lyle⁵⁷ as follows —

- 1 Q₃ must be at least 25 per cent of the largest excursion of QRS in any lead
- 2 There should be no associated right axis deviation
- 3 R₃ must be present and S₃ absent.
- 4 QRS₁ must not be M or W shaped
- 5 A coronary Q₃ is usually accompanied by a Q₂
- 6 A small upward deflection of less than 1 mm before a deep Q₃ usually takes the Q out of the coronary class
- 7 A deep Q₃ disappearing on deep inspiration is always of postural origin, though a failure to disappear is no proof of infarction if the other criteria are not satisfied

Dressler⁵⁸ thinks that a T₁ smaller than T₃ is suggestive of myocardial infarction. Sharpy-Schafer^{59 60} has shown that T inversion due to myocardial infarction is further inverted after raising the value of serum potassium while a T inversion due to preponderance of a ventricle or that due to thyroid deficiency becomes upright after administration of potassium. Even when an E C G is negative and the clinical history very strongly suggestive of coronary disease, the E C G should be repeated after a few hours or if the patient's condition permits the anovaemia test of Levy³⁷ or the standard two-step exercise of Master³⁸ should be carried out and the alterations in the E C G should be looked for. In the present series there are four cases where the first E C G taken within a few hours of the clinical evidences of the attack was normal but on repeating the E C G after 24 hours, during which there was no recurrence of symptoms, definite changes of myocardial infarction were found. Only 54 of the 82 cases could be subjected to an electrocardiographic study. The difficulty of obtaining the paper and the cells during the war years was mainly responsible for this shortcoming. Of the 54 patients 30 had evidences of anterior infarction 20 had evidences of posterior infarction and in the remaining 4 the E C G was not characteristic of an isolated anterior or posterior infarct.

Leucocytosis There is a leucocytosis as a result of the infarction in a large majority of cases but it takes about 36 to 48 hours to appear in some cases. In the 82 cases here reported the W B C count was done in 53 patients and in only 8 of these was it within normal limits (15.2 per cent). In 25 (47.5 per cent) the leucocytes were between 800/cu mm and 10,000/cu mm, in 19 (36.1 per cent) between 10 and 15,000/cu mm, and in 1 case it was as high as 25,500/cmm. The leucocytosis was invariably a polymorphonuclear one and was found in all 45 patients in a varying degree.

Erythrocyte sedimentation rate Increase in the E S R appears later than fever or leucocytosis but persists for a longer time. It is in some measure an index of activity in the infarcted area. However, if congestive cardiac failure supervenes the sedimentation rate usually becomes slow. Of the 39 cases in this series where the E S R was estimated it was found to be raised in 27 (67.5 per cent). Unfortunately the E S R was not repeatedly estimated in a number of cases, where it was not accelerated otherwise the figures of increase would have been very much higher. The acceleration varied from 15 mm/hour to 110 mm/hr.

Radiological diagnosis Levene⁶¹ and his co-workers reported in 1938 a diminution of systolic-diastolic excursion in a localised area, a loss of convexity of the left border of the heart, and an associated increase in the transverse diameter of the heart were the radiological criteria for the diagnosis of coronary occlusion. In 1941 Levene⁶² compared the accuracy of radiological diagnosis as checked by the necropsy findings in 38 cases against the E C G and found them to be 89.5 per cent and 94.7 per cent respectively. However, as far as a correct localisation of the site of infarct was concerned the radiologist obtained a percentage of 72.7 per cent against 54.5 obtained with the E C G. Other radiological evidences of coronary occlusion which may be met with are a reversed localised pulsation, aneurysm of the heart and patches of calcification in the coronary artery or a devitalised area of the myocardium.

Other lesser known diagnostic aids are a delay in the arm to tongue circulation time as reported by Selzer and the hyperactive cardio-inhibitory carotid sinus reflex. Sigler who carried out a comparison between the accuracy of this reflex response and the E C G findings in 1078 cases found that response was positive in 91.3 per cent of males and 72.6 per cent of females as against an E C G diagnosis in 63 per cent of males and 71.9 per cent of females.

Diff. Diagnosis Of the conditions like angina pectoris, acute pericarditis, acute pleurisy, pleurodynia, pulmonary embolism, spontaneous pneumothorax, biliary disease, peptic perforation, chronic cholecystitis, acute pancreatitis and others which may present difficulties in the diagnosis of acute coronary occlusion, pulmonary embolism is perhaps the one which causes greatest confusion. Not only the physical signs and symptoms but also the E C G picture may be confusing. Acute cor pulmonale shows deep S1 and Q3 and a negative T3, bundle-branch-block of type II, with a broad shallow S1 and S2 or a marked depression of ST1 and occasionally ST2. The T-waves are likely to be inverted from the right side of the precordium but may be normal in CF4 and CF5 positions. The E C G changes resemble very much the Q3 T3 type of diaphragmatic infarct and are supposed to be due to an ischaemia of the right ventricular musculature resulting from diminished coronary flow due to increased ventricular cavity pressure and the production of right heart strain. The conditions can only be differentiated if one thinks of the possibility of pulmonary embolism in a patient who has been immobilised by illness or operation or has history or signs of trauma or infection of the lower limbs or has any other detectable source of embolism. And yet we cannot insist on the last factor because it is possible to have phlebothrombosis

without thrombophlebitis and either condition may be deep enough to escape detection. A raised icterus index, a positive electrocardiographic pattern of acute cor pulmonale and a positive radiological evidence of pulmonary infarction would establish the diagnosis.

Complications Of the various complications of coronary occlusion intercurrent pneumonitis, thrombosis of cerebral arteries or veins of the inferior extremities and the various embolic manifestations are the more frequent. Pneumonia accounted for 33 per cent of the deaths in a series of 128 reported by Woods and Barnes,⁴⁹ whereas cerebral thrombosis occurred in 15 per cent of their fatal cases and 2.9 per cent of the survivals and massive pulmonary embolism occurred in 10 per cent. Four years later Nay and Barnes⁶⁶ reported an incidence of 87 per cent for embolic and thrombotic complications in a series of 100 from the Mayo Clinic. Pulmonary embolism was found in 14, cerebral embolism or thrombosis in 8, thrombophlebitis in 7 and peripheral arterial occlusion in 4 cases. They maintain that common cause for embolism is not the heart but the veins of the lower limbs, particularly when embolism coincides with the first movements.^{49, 66} 87 per cent of the cerebral vascular complications occurred between the 4th and the 20th days and 86 per cent of the thrombophlebitis between the 10th and the 16th days, periods when the blood pressure is at the lowest levels. The danger of embolism from the heart arises when auricular fibrillation is an associated phenomenon. Askey and Neurath⁶⁷ found that 33 per cent of the patients that developed auricular fibrillation after the attack and 57 per cent of those who had it before the attack died of evident systemic embolism. Ravdin and Wood⁶⁸ describe an interesting case of a physician aged 32 who 11 days after the onset of acute coronary occlusion developed tingling and numbness in both his lower extremities which soon became cold and blue. The patient made a diagnosis of embolism of the abdominal aorta and immediately summoned Ravdin who removed an embolus obstructing the mouths of the common iliac arteries. The patient was put on heparin for 11 days and made a complete recovery. Another complication is aneurysm of the heart following coronary occlusion. Applebaum and Nicholson³⁹ report 57 of such cases. In 9 of these the aneurysms ruptured with a fatal result. Mallory and his colleagues¹⁷ found cardiac rupture in 8 of their 72 necropsies. Aneurysm of the coronary artery is another rare complication of which 31 authentic cases were recorded by Packard and Weschler.⁶⁹ Persistent pain in the left shoulder region lasting for a few weeks to 2 years has been described by Ernsten and Kinell⁷⁰ in 17 cases. A similar pain may occur in latent coronary occlusion and may thus afford a clue to diagnosis. In the present series one case had cerebral thrombosis, and one had anuria for 4 days. There was only one case of pulmonary embolism.

Course and Prognosis Excluding those that die instantaneously or before receiving any medical aid the mortality of acute coronary occlusion is about 25 to 30 per cent within the first six weeks according to the recent figures. However, there is no other task more difficult or more likely to damage the prestige of a physician than that of prognosticating the course and the outcome of a given case of acute coronary occlusion at an early stage. No one symptom or sign, individually or in combination with others is of any definite prognostic

significance at the start. A remarkable complete functional recovery is possible after an attack of acute coronary occlusion. Sir James MacKenzie lead an active life for 25 years after his attack and Lewis,⁷¹ Cassidy⁸ and several others have recorded of cases leading a life of more active physical and mental exertion for years after coronary occlusion. Bland and White⁷² in a series of 200 cases of coronary occlusion found that about one fourth survived the 10 year period. Of the 66 patients who survived their attack Smith Sauls and Ballew⁷² followed up 36 for 3 years or less, 16 for 3 to 6 years, 12 for 6 to 9 years and one for as many as 23 years.

Though no definite prognosis can be given from the early data in a given case, the frequent recurrence of pain, rapid onset of heart failure, persistence of the signs of shock and a very low pulse pressure, the occurrence and persistence of frequent multifocal extra-systoles, auricular fibrillation and the other arrhythmias are all looked upon with increased anxiety. Master, Dack and Jaffe⁷³ found the immediate mortality in a group of 375 cases to be 25 per cent, Woods and Barnes⁴⁹ had a six week mortality of 47 per cent in their 108 cases and Coroner and Halt⁷⁴ report an immediate mortality of 16.2 per cent in 287 patients. On the other hand Newmann¹⁴'s mortality rate in 50 service personnel was as high as 78 per cent. The immediate mortality in the present series was 26 (81.7 per cent) amongst the 82 patients. 42 were discharged relieved after a stay of more than six weeks in the hospital whereas 14 cases went home against medical advice within three weeks of admission.

Influence of the different factors on prognosis. Age. More advanced the age more serious is the prognosis. The mortality figures according to the various age groups in this series and the series reported by Woods and Barnes⁴⁹ are summarised in Table 15.

TABLE 15 Age and mortality

| Age | Below 30 | 30-39 | 40-49 | 50-59 | 60-69 | 70 & over | Total |
|--------------------|----------|----------|---------|-----------|--------|-----------|-----------|
| Total no. of cases | 4 | 16 | 38 | 16 | 8 | 1 | 82 |
| No. expired | Nil | 3(18.7%) | 10(26%) | 10(62.5%) | 2(25%) | 1(100%) | 20(81.7%) |
| Woods & Barnes | | 28% | 41.7% | 41.7% | 57% | 85% | 47% |

Sex. Females fare less favourably than males, partly because they belong to the older age groups. In their series of 200 cases Bland and White⁷² found that twice as many women as men died during the first four weeks. Woods and Barnes⁴⁹ found the mortality rate of females to be 75 per cent as compared to 42 per cent in the males. The very small number of females in this series do not permit any conclusions to be drawn but the female mortality in this series was 8 out of 9 cases (88 per cent).

Blood pressure. Pre-existing hypertension has not satisfactorily been proved to influence the prognosis in any adverse fashion, as shown by Master, Dack and Jaffe.⁵⁴ On the other hand the fall of systolic pressure during the attack is an index of the extent of shock and a fall of systolic pressure to 80 mm. or below is of series prognostic significance, though recovery is by no means unknown.²⁵ A fall in the pulse pressure is perhaps a better guide to prognosis. In a series worked out by

Master, Dack and Jaffe⁷⁵ it was found that when the pulse pressure was between 49 and 80 mm of Hg the mortality rate was 19 per cent, with a pulse pressure of 29 to 20 mm it was 28 per cent and with a pulse pressure below 19 mm the mortality was as high as 52 per cent. In another series of 588 attacks reported by Master²⁵ the mortality in the hypertensives was found to be 54 per cent as compared with 78 per cent in those who did not have hypertension.¹¹ Bain⁷⁶ on the other hand considers hypertension as an increased liability especially if it is associated with enlargement of the heart. In our series 8 of the 33 hypertensives expired (24.2 per cent) as compared with 36.7 per cent mortality in the non-hypertensives. When everything is taken into consideration, it appears that hypertension per se does not significantly affect the course of the disease during or after the attack. It is difficult to predict the course of blood-pressure in a given case of coronary occlusion but it is more difficult to predict the course of a case from the blood-pressure readings.

Angina The previous incidence of angina does not make any material difference after an attack of acute coronary occlusion. Woods and Barnes⁴⁹ found the previous incidence of angina to be 39.7 per cent and 40 per cent in the survivals and the fatalities respectively. On the other hand, given a preliminary warning in the form of angina, an acute myocardial infarction could at least be delayed and minimised, if not entirely avoided, by measures which would diminish the cardiac load, dilate the coronary vessels and give time for the development of anastomotic circulation. In this series two of the 14 patients who had angina succumbed (14.3 per cent) to their disease.

Arrhythmias Extrasystoles are of frequent occurrence in acute coronary occlusion and by themselves do not materially affect the prognosis but multifocal and paroxysms of extrasystoles and disturbances of intra-ventricular conduction increase the possibility of an unfavourable termination. Master and his colleagues⁷³ found that in 57 of their 375 cases, where the QRS interval was 0.12 sec or more the mortality was 42 per cent as against 23 per cent in the rest. Similarly the occurrence of auricular fibrillation raised the mortality from 41.3 per cent in those that were free from it to 89.4 per cent in the affected ones in a series of 1247 patients reported by Asky and Nourath.⁶⁷ In the series here presented both the cases of gallop rhythm and one of tic-tac rhythm expired.

Recurrence of attacks A repetition of an episode of acute coronary occlusion makes the outlook more serious. The mortality in second attack was found to be 60 per cent as against 34 per cent in the primary attack by Smith, Sauls and Ballew.³¹ Of the 16 cases of Fisher and Zukermann²⁴ that had a recurrent attack 11 died at the second attack and four at the third. In the present study 13 cases had a history of one previous attack and only 2 of these expired whereas one patient who had two previous attacks survived the third one probably to fight another one at some future date.

Rehabilitation Unfortunately follow-up of cases is our shortcoming and unless we remedy this we cannot throw much light on the problem of rehabilitation. Master and Dack⁷⁷ reporting follow up of 415 patients of acute coronary occlusion find that 53 per cent of all survivals returned to their work, 32 per cent to full time and 21 per cent to part

time work 75 per cent in the fourth decade, 54 per cent of males and 51 per cent of females, 57 per cent of office patients and 46 per cent of hospital patients, 84 per cent of professional people and 50 per cent of non-professionals could return to their work 59 per cent resumed work after the first attack, only 38 per cent after the second attack and not more than 23 per cent could do it after the third attack Of those who resumed work 54 per cent did it within 3 months, 76.5 per cent within six months and 92 per cent within a year 56 per cent of this rehabilitated population had some degree of residual angina, dyspnoea or weakness

(My thanks are due to the Datta K E M Hospital and Seth G S Medical College and the Honorary Physicians of the K E M Hospital for permission to use the Hospital records and to report on cases under their care)

DISCUSSION

Dr C B Dhurandhar wanted to know what was the confirmatory test for the diagnosis of early cases of arteriosclerosis He added that few cases could be definitely diagnosed from an examination of the fundus whereas in others a probable diagnosis was arrived at from the symptomatology

Dr N K Sahar enquired as to the criteria of the diagnosis of coronary occlusion in the child of 9 years He reported a case where fat embolism simulated coronary occlusion He also cited a case where rupture of the myocardium followed a primary coronary occlusion and which was mistaken for a second attack

Dr Abdul Hameed agreed with the speaker about the incidence of coronary occlusion in a younger age group He also mentioned that heredity played a part in the etiology of the disease

Dr J K Mehta enquired what the procedure should be in cases where the clinical history was suggestive of coronary occlusion but the E C G did not show any change

Replying to Dr Dhurandhar the speaker said that in 13 cases with definite evidence of arteriosclerosis 8 showed evidence of arteriosclerosis at the autopsy He added that besides the examination of the arteries in the fundus or a muscle section, no other method of detecting arteriosclerosis at an earlier stage was known so far

With reference to Dr Sahar's question regarding the evidence of coronary occlusion in the child aged 9 years, speaker stated that a history of previous rheumatic infection and E C G suggestive of a posterior wall infarct was obtained on four different occasions over a period of four weeks and a completely negative radiological examination of the lungs was considered adequate for the diagnosis The only other condition that could be thought of was a congenital stenosis of the right coronary which would produce a similar picture with a functional coronary insufficiency as the child grew up

Replying to Dr Hameed, the speaker said that as far as the hereditary influence in cardiovascular diseases is concerned, statistics in Europe and America supported the conception, but unfortunately this study could not be carried out in patients in this country

With reference to Dr Mehta's question the speaker suggested a second E C G after a few hours, or with lead IVF and R

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Critical Notes and Abstracts

STREPTOMYCIN THERAPY—Hinshaw says that the Committee on Therapy of the American Trudeau Society and its Subcommittee on Streptomycin Therapy has, during the past year, carried out a series of therapeutic trials of streptomycin therapy in tuberculosis. In addition, the committee has reviewed results of therapeutic trials conducted by the United States Veterans Administration, the United States Army and the United States Navy and has reviewed results of work previously undertaken at Cornell University, Mineral Springs Sanatorium and the Mayo Clinic. The committee is collaborating closely with the Committee on Medical Research of the National Tuberculosis Association. The following conclusions and recommendations appear to be justified on available evidence.

1 Intensive parenteral and intrathecal streptomycin therapy is advised for treatment of tuberculous meningitis. Although remissions are induced frequently by such treatment, subsequent relapse is likely to occur. Early diagnosis and prompt treatment appear to yield superior results, hence treatment must be instituted frequently before complete bacteriologic data are available.

2 Streptomycin therapy is advised for treatment of acute hematogenous miliary tuberculosis. Prompt treatment is necessary if best results are to be realized. Physicians are warned that non-tuberculous pulmonary infiltrations may simulate miliary tuberculosis roentgenographically. Nevertheless, if treatment of miliary tuberculosis is to be prompt, it may have to be instituted before bacteriologic confirmation of diagnosis is available.

3 Streptomycin therapy is advised for the treatment of severe cases of tuberculous laryngitis and ulcerating tuberculous lesions of the mucous membranes of the oropharynx. The palliative clinical benefits of such treatment are sufficiently uniform and gratifying to justify trial of treatment even in some instances when the ultimate prognosis of associated pulmonary tuberculosis appears grave. Combined parenteral and topical treatment is suggested, pending more complete information as to the relative merits of these two methods of administration.

4 Streptomycin therapy is advised for treatment of progressive ulcerating tuberculous lesions of the tracheobronchial tree. Streptomycin should not be expected to benefit fibrous strictures of the tracheobronchial passages. Parenteral treatment should be employed in such cases. It is not clear as yet whether results are superior when combined aerosol and parenteral treatment is used.

5 Streptomycin therapy is not indicated at this time for treatment for all types of pulmonary tuberculosis. However, tuberculous pneumonia should be treated with streptomycin. It is not recommended that such lesions be treated unless the physician has reason to believe that conventional therapeutic methods will not suffice.

Streptomycin cannot be recommended at this time for treatment of (a) chronic fibroid or fibrocascous pulmonary tuberculosis, (b) acute destructive and apparently terminal types of pulmonary tuberculosis, (c) minimal or early moderately advanced pulmonary tuberculosis with favourable prognosis. These recommendations may be modified by subsequent experience, especially if the toxic effects of the drug are

found to be avoidable. It is important that tuberculosis with favourable prognosis be not treated with streptomycin until the significance of toxicity and drug fastness is better known or means of avoiding them are found

6 Streptomycin therapy is suggested for further trial as a remedy for the symptoms of acute ulcerative tuberculous enteritis

7 Streptomycin is recommended for treatment of tuberculous draining cutaneous sinuses and appears to be highly effective in a large majority of cases

8 Streptomycin is not recommended for treatment of chronic empyema that is of tuberculous origin because of its apparent ineffectiveness

9 More extensive observations will be required to learn whether streptomycin is of sufficient value to justify its use in (a) prophylactic treatment before and after surgical procedures, (b) treatment of tuberculosis of the genitourinary tract, (c) treatment of tuberculosis of the bones and joints, (d) treatment of tuberculosis of the skin, (e) treatment of tuberculous lymphadenitis without sinus formation, (f) treatment of ocular tuberculosis

10 Streptomycin, like many other useful drugs, has definite toxic potentialities. A disturbance of vestibular function will be observed frequently, especially following prolonged treatment with larger doses. Deafness may result in rare instances when the excretion of streptomycin is defective, but hearing is usually regained if treatment is suspended. Serious renal damage may result from streptomycin when there is pre-existing renal disease. Cutaneous rashes apparently due to acquired hypersensitivity to streptomycin are occasionally observed and sometimes indicate that treatment should be suspended temporarily

It has not been fully determined what the minimal effective therapeutic dose of streptomycin may be, nor is it known how dosage should be modified to secure optimal results in each of the many different types of tuberculosis. It is suggested that the total parenteral dose in twenty-four hours may be from 1 to 2 Gm.

Streptomycin treatment should be avoided when other treatments are available because to produce a drug resistant strain of tubercle bacilli by such treatment may possibly make this form of treatment ineffective should a more serious type of tuberculosis subsequently develop

(Hinshaw, H. C. Mayo Clinic Rochester, Minnesota. J. A. M. A. 135: 641-643, November 8, 1947)

PATHOGENESIS AND TREATMENT OF ULCERATIVE COLITIS WITH EXTRACT OF HOG STOMACH—Ehrlich

asserts that with few exceptions such as amebic and bacillary dysentery and tuberculous enterocolitis, ulcerative colitis is a nonspecific disease. Proteolytic enzymes are present in the colon and rectum. Gastro-intestinal hypermotility whether it be neurogenic, psychogenic or gastrogenic increases the delivery of proteolytic enzymes into the colon, thus predisposing the colonic mucosa to autolysis.

It is presumed that the colon normally contains an anti-proteolytic or protective substance to inhibit dissolution of the mucosa. This anti-proteolytic substance seems to be particularly deficient in the

descending colon and rectum under the mentioned circumstances, thus upsetting the proteolytic, anti-proteolytic enzymatic balance predisposing the individual to mucosal autolysis. Dessicated extract of hog stomach appears to contain this anti-proteolytic substance.

Fifteen cases of idiopathic ulcerative colitis are reported in which extract of hog stomach was administered. An average dose of 40 Gm was given in divided doses before meals. In the protracted and fulminating cases, the initial dose was always 60 Gm daily, it was gradually reduced as amelioration of symptoms and endoscopic improvement resulted. At least six ounces of liquid should be taken with or immediately following its administration.

The dosage was not reduced until adequate resolution was evident by endoscopic visualization. Each case was sigmoidoscoped at weekly intervals during the active phase, then once monthly. A maintenance dose of 10 Gm three times daily was continued for from one to four months. Edema, inflammation, spasm and ulceration subsided under the influence of the hog stomach extract. Four patients required sulfonamide therapy for secondary infections.

(Ehrlich, R. Boston, Mass. *American J of Digestive Diseases* 14: 294-297 September, 1947.)

PENICILLIN IN CARDIOVASCULAR SYPHILIS. EARLY REACTIONS TO ADMINISTRATION—Tucker and Farmer think that a full evaluation of the results of penicillin therapy in cardiovascular syphilis will require observations on treated patients over a period of many years. At present, it is possible to analyze only the early reactions to administration of penicillin.

In early syphilis and in neurosyphilis the Jarisch-Herxheimer reaction ("therapeutic shock") is a frequent immediate effect of penicillin therapy. This phenomenon is of potential importance in cardiovascular syphilis because of the theoretic possibility of the occlusion of the coronary orifices or of the rupture of an aneurysm.

The authors think that it is important to determine whether special precautions are indicated not only from the standpoint of treatment of patients with recognized syphilitic cardiovascular disease but also because patients with cardiovascular syphilis are frequently given penicillin for other conditions, such as concomitant neurosyphilis, benign late syphilis or intercurrent acute infectious disease.

They have attempted to clarify this problem by presenting a preliminary estimation of the incidence and severity of untoward reactions occurring during the administration of penicillin to patients with cardiovascular syphilis.

Twenty-two patients with syphilitic aortic insufficiency and eight with thoracic aortic aneurysm were treated by the intramuscular route with sodium penicillin in aqueous solution in total dosages ranging from 2,000,000 to 15,000,000 Oxford units.

Five patients had fever (100.0 to 102.4°F) within the first 16 hours of treatment. Two patients with long-standing angina at rest had attacks of usual severity and frequency during and subsequent to administration of penicillin. In no instance was the treatment schedule interrupted. No significant differences in the incidence of febrile reactions or cardiovascular symptoms occurred in nine patients receiving small initial doses (500 to 3,000 Oxford units) as compared with that in

21 patients given large initial doses (25,000 to 100,000 Oxford units) of penicillin

The authors conclude that the absence of reported severe reactions tends to confirm their impression that the dangers of severe untoward reactions may have been unduly emphasized. More work must be done with various dosages of penicillin in patients with cardiovascular syphilis, however, before final conclusions are justified.

Since this paper was submitted, four additional patients with cardiovascular syphilis (one with aneurysm and three with aortic insufficiency) were treated with initial doses of 50,000 to 100,000 Oxford units of crystalline penicillin G. Neither febrile Herxheimer reactions nor untoward symptoms referable to the cardiovascular apparatus were noted.

(Tucker, Harold A., Johns Hopkins Hospital, Baltimore, Md. and Farmer, Thomas W., Arch Intern Med. 80: 322-327 September, 1947.)

HYPERVENTILATION SYNDROME by HADDON M. CARRER, M.D., *Mayo Clinic, Rochester*

THE ROLE OF HYPERVENTILATION CAUSING MILD RESPIRATORY ALKALOSIS IN FUNCTIONAL DISORDERS*

Hyperventilation as a cause for phenomena that are seen daily is so common that one may overlook its importance. All people will at some time have hyperventilation owing to stimulation of the respiratory center by mental excitement or as a result of reflex stimulation by pain, heat or cold. The latter instance, perhaps, answers a physiologic demand as a part of an "alarm" reaction. From these responses which occur in normal persons, there is a gradation which extends through persons who are working under a temporary strain on an entirely adequate amount of nervous stamina to inadequate persons who have stamina only for the ordinary method of living. Among the group of stable subjects are airplane pilots and combat soldiers who are facing danger. The relatively unstable group embraces a wide variety of exhausted and psychoneurotic patients. This paper is primarily concerned with the latter group of persons and the frequency with which hyperventilation influences symptoms present in this group.

Under normal circumstances, there is a reservoir of carbon dioxide in the alveoli of the lung. This is essential to the well-being of the body. The chemical reactions of the body are quickly altered by changes in concentration of the carbon dioxide in the alveolar air. Normally, in the alveolar air the carbon dioxide approximates a partial pressure of 40 mm. of mercury. Under circumstances of affecting the depth or the rate of respiratory excursion by increasing either, there may be rapid fall to a partial pressure of 20 mm. of mercury—or to approximately half of the normal value for the carbon dioxide in the alveolar air.

The decrease in the concentration of carbon dioxide in the alveolar air may be achieved by several mechanisms. Forced breathing to increase the depth or rate of the respiratory excursion will, for experimental purposes, bring about this state. The sighing and yawning frequently noted in people who are excessively anxious bring about

* Recently, the Editor has seen in consultation several cases of fits 'tetany' 'catatonla' etc which were in fact manifestations of Hyperventilation of functional origin. As there is little about this syndrome in the standard text books, this comprehensive article by Carreyer is reprinted here from Proceed Staff Meet Mayo Clinic, 21: 301-367 (Sept 18) 1940.

similar changes. Possibly the increased respiratory excursions necessary to obtain adequate oxygen at rarefied atmospheres will cause, as a side effect, symptoms arising from the loss of carbon dioxide in the alveolar air. Violent exercise in an individual unaccustomed to such activity may effect such changes.

The loss of carbon dioxide in the alveolar air brings about alkalosis within the body. This alkalosis is responsible for the clinical symptoms precipitated. As hyperventilation takes place and the concentration of carbon dioxide in the alveolar air falls, there is a progression of subjective and objective changes which, if their nature is not understood, will lead to grave apprehension, especially by relatively unstable patients. The first symptom experienced is *lightheadedness*. As this sense of *giddiness* grows more pronounced it makes the patient feel that *fainting* is imminent. The patient frequently will go out of doors, open a window or fan himself. A sense of *in steadiness*—at first entirely subjective—may then ensue. As the syndrome progresses, an insatiable sense of *air hunger* develops. Patients often express themselves by such statements as, "The air won't go down far enough," "Air is doing me no good," or "I can't get a satisfactory breath." *Pressure sensations* within the thorax often cause alarm, and, for the physician, necessitate careful consideration to exclude pain arising from coronary artery disease. The sensations noted with the hyperventilation syndrome characteristically occur when unusual physical effort is not being expended. These sensations occur most commonly when the patient is inactive. They seem to be relieved in part by manual pressure on the thorax. Patients will often state that pressing on the walls of the thorax produces some relief.

This state is followed by a pretetanic condition that is associated with a sensation of *tingling in the extremities*. This usually assumes stocking and glove distribution, it begins peripherally and extends proximally. The more prolonged and intense the hyperventilation, the more marked is the paresthesia. An increased excitability of the muscles of the body is evident in the pretetanic phase. Spontaneous *twitching of isolated muscle groups* will occur. Judgment and skill in acts requiring finely coordinated movements will be seriously impaired.

With further hyperventilation, spontaneous tetanic contractions of the muscles will be noted. These begin as *carpopedal spasms* similar to those observed in tetanic states caused by other conditions. In advanced degrees of tetany, opisthotonos may also be seen. The nature of the *tetany* produced is as yet a question. Probably there is a decrease in the amount of ionized calcium caused by the binding effect of the relatively greater quantity of available base. Chemical examinations have failed to demonstrate consistent changes in the total value for serum calcium. The decreased quantity of available calcium ion exaggerates the excitability of the neuromuscular mechanism.

As was stated, responses of the nervous centers of respiration may arise through lower reflexes initiated by contact of the body with heat, cold or painful stimuli. Likewise, these responses of the respiratory center may result from cerebral excitement.

The hyperventilation syndrome arising primarily in the cerebrum occurs in two forms. One form is associated with periodic sighing and

struggling for an adequately deep breath, the other form is associated with the so called acute anxiety attack. Maytum and Willius have emphasized the clinical importance of these abnormalities of breathing in the differential diagnosis of diseases of the heart and lungs.

A short while ago, Walsh, in considering attacks of acute anxiety attributed their occurrence to the periodic release of pent-up anxiety. This physiologic psychiatric consideration may be supplemented by analysis. It would appear that an attack of acute anxiety consists of symptoms resulting from hyperventilation in addition to those caused by response to fright, which is characterised primarily by a release of epinephrine within the body.

Hyperventilation associated with respiratory alkalosis is a terrifying experience to a patient who has a poor understanding of his symptoms. Relatively unstable persons are most commonly affected. Psychoneurotic patients with anxiety are particularly subject to this respiratory derangement.

Attacks of hyperventilation commonly occur in places where great embarrassment would be experienced should an unpleasant scene be caused, that is, in the front pews of a church, in crowds, in the presence of guests who are difficult to meet, and preoperatively in a hospital. On feeling lightheaded and fearing syncope, patients will, through further hyperventilation, attempt to "fight off" the strange sensations they are having.

Emotional experiences of grief, fear, anger and love are associated with respiratory stimulation. The act of crying seems to be made easier by hyperventilation. I have often seen a child, thinking tears were warranted but finding them not quite spontaneous, facilitate crying by taking a few deep breaths.

After World War I, White and Hahn came to the conclusion that the hyperventilation syndrome was responsible for neurocirculatory asthenia. Of a large group of healthy subjects, sighing respiration occurred in only 19 per cent. This respiratory abnormality was noted in 80 per cent of a group of patients who had neurocirculatory asthenia. Several medical officers with whom I have spoken have expressed the opinion that the hyperventilation syndrome occurred very frequently in the recent war but it usually was not recognised.

Hyperventilation with resulting in co-ordination and impairment of judgment represents a condition of considerable importance in aviation. This relationship has been emphasized by Rushmer, Hinshaw, and Boothby. Hinshaw noted such a phenomenon when as an inexperienced pilot he encountered technical difficulty in flying. When he recognized that he was suffering from hyperventilation, and corrected the abnormal breathing the lightheadedness, confusion and pretetanic paresthesia promptly subsided.

On two occasions I have had reported to me evidence of near tragedy as a result of hyperventilation in amateur pilots of airplanes. One pilot became confused after he had experienced technical difficulties and attempted to land his ship when at an altitude of approximately 1,000 feet. The other pilot, likewise confused by hyperventilation while piloting a plane, scarcely missed hitting a barn although he had considered that his altitude was in excess of 500 feet.

The treatment of the hyperventilation syndrome depends largely on its recognition. A discussion with the patient of the changes brought about by hyperventilation, followed by a demonstration with the reproduction of the patient's symptoms is an important part of therapy. The most anxious patient appreciates the physician's demonstration that the terrifying sensations are not imaginary. He develops confidence that his condition is understood, and becomes willing to discuss any underlying psychic factors. In many cases, all that is necessary is to demonstrate that the symptoms are the result of hyperventilation and to explain the nature of the symptoms to the patient. In other cases, the anxiety is more deeply motivated and prolonged psychiatric investigation and treatment may be indicated.

One should instruct the patient to hold his breath or, preferably, to rebreathe air from paper sack. These procedures allow carbon dioxide to reaccumulate in the alveolar air.

REPORT OF CASE

A Jewish woman, of Polish extraction, who was thirty six years of age, was referred to this Clinic, in October, 1945, because of hysteria. She complained of troublesome weak spells which had occurred intermittently for seven years. Her past history and family history were essentially negative. She had two children who were eight years and two and a half years of age, respectively. She was utterly exhausted by her responsibilities, particularly those of caring for the children.

She said that the spells occurred at various intervals but usually occurred several times weekly. They would appear during her waking hours but would not disturb her sleep. A prodromal period of five to fifteen minutes would usually precede the onset of the attack. During this time she would try to "fight off" the attack, primarily by hyperventilating her lungs. The attacks were initiated by lightheadedness, weakness, and tingling of the extremities. Quickly a sense of profound air hunger would develop and a sensation which she described as "stiffness" would appear in her extremities. Repeated sighing and yawning were often noted in this stage of the attack. She would then enter an unresponsive state from which she could not be aroused easily.

She would lie down with her eyes closed tightly and remain in this position for a period of several minutes to an entire day. While she would be aware of conversation in her presence, she would be unable to respond to questions. She never had lost consciousness and convulsions had not occurred although a "quivering" had been noted, especially in the legs.

These attacks would occur more commonly if the patient was very tired or if she was tense. Arguments and meeting people particularly predisposed to these episodes. Disturbing news received over the telephone would frequently precipitate an attack. At no time was she placed in jeopardy by the onset of the attacks, she could always "fight them off" until she could reach a safe haven.

Her blood pressure was 150 mm of mercury systolic and 98 mm diastolic. There was no evidence of inadequate cardiac or renal function. Erosion of the uterine cervix was found and appropriate treatment was instituted. Seasonal hay fever and asthma had been somewhat troublesome for five years.

Urinalysis, hematologic examination, a serologic test for syphilis, and roentgenologic examination of the head and thorax did not disclose any abnormality. No evidence of intracranial pressure was noted on funduscopic examination. The results of neurologic and physical examinations were negative. Chvostek's and Trousseau's signs were not present.

After the nature of hyperventilation and its effect on the production of the symptoms had been explained to the patient, a demonstration was made. The patient was asked to breathe deeply and somewhat rapidly. After approximately thirty second of such breathing she stated that she was experiencing sensations in the head and extremities like those she had noted during the prodromal phase of her attacks. Suddenly, she screamed loudly, fell backward on the dining table and began to breathe forcefully. She resisted attempts to restrain her mouth.

a paper sack provided for rebreathing air. In a moment this tumultuous breathing was supplanted by shallow, rapid breathing which continued for ten minutes. No tetany of the extremities was noted. Attempts to open her tightly closed eyelids were resisted.

Since such a state frequently had lasted an entire day, methods of suggestion apparently were necessary to interrupt the attack of hysteria which had been precipitated. Suggestions were made to the patient by conversation with a third party who was present. The mechanism of hyperventilation was explained. It was stated that on placing a paper bag over the nose and mouth approximately ten deep breathes would be required to interrupt the state of hyperventilation. The patient took ten deep breathes. It was then said that the tenth breath would be held, and it was. The paper sack was removed. The patient sat up with her eyelids still closed tightly. It was suggested that the attack would end in a few moments, the patient was aroused a short time later and was again normal. She commented that she felt as though she had been hypnotized.

Subsequent correspondence reveals that she has not had any more attacks. This has been made possible by scrupulous avoidance of hyperventilation.

COMMENT

An analysis of this case indicates that the psychoneurosis was probably primary and resulted in hyperventilation. The hyperventilation, in turn, produced physiologic symptoms that increased her anxiety and made her less secure. The syndrome of hyperventilation was elaborated and on it was imposed a hysterical super-structure. As a result, a vicious circle developed. An important factor in the treatment was a demonstration that the symptoms were directly due to hyperventilation.

Notes on New Drugs and Preparations

KEMITHAL SODIUM

Name of Drug 'KEMITHAL' SODIUM

Chemical Composition The sodium salt of 5- Δ^2 cyclohexenyl-5 allyl 2 thio-barbituric acid

| | | |
|---------------|--|--|
| <i>Dosage</i> | For induction of anaesthesia — 0.5 to 1.5 Gm | } Used intravenously as a 10% solution |
| | For short anaesthesia — 1 to 2 Gm | |
| | For prolonged anaesthesia — 0.5 to 1.5 Gm for induction, followed by 0.2 Gm as required | |

Indications Basal hypnosis and anaesthesia of short or prolonged duration

Contraindications No contraindications, other than those common to all short-acting intravenous barbiturates, have been found

Toxic symptoms Respiratory depression follows over dosage

Packings Ampoules of 1 and 2 Gm — containers of 5 and 25 each, with sterile pyrogen free water

Ampoules of 5 Gm — containers of 5

Manufactured by Imperial Chemical (Pharmaceuticals) Ltd., Manchester
and

Distributed by Imperial Chemical Industries (India) Ltd.

Original Contributions

THE WORLD OF MEDICINE—ONE WORLD

by

ROBERT HEILIG, MD, MCF, FNI

Chief Physician, Sawai Man Singh Medical College Hospital, JAIPUR

(Continued from page 32)

The work of Galen who, inspite of a tremendous practice, found time for copious writing became literally the Bible of world medicine for the next 1,300 years. He incorporated in his numerous books all that was known in his life time of anatomy, which mainly was animal anatomy, of physiology, which pleased the Catholic Church for centuries afterwards so much that everyone doubting any point of it was persecuted as a heretic, this was due to Galen's concept that the body is significant only as a servant of the soul, which he localized in the brain. His opinions are based partly on vivisection of which he was a master, partly shaped to suit preconceived ideas, this latter weakness led to mistakes and it took tremendous courage and the life work of some of the best scientists of the 15th and 16th century to correct them. Until then, nobody doubted his authority and Sylvius, the teacher of the great Vesalius, rather assumed that the human body had changed, than to concede that Galen might have committed a mistake. Still more dogmatic was Galen in his treatises on pathology and treatment which was entirely subordinated to his tendency to over-systematisation. What did not fit into his logical system was wrong and every problem could be solved by applying a few simple principles of Aristotelian logic. In this sense, Galen marked a serious retrogression compared with Hippocrates and the earlier Alexandrians, but the completeness of his encyclopaedic writings, which cover every corner of medical science and art, is admirable and of greatest importance for our knowledge of Graeco-Alexandrian medicine. His death coincided with the end of Roman world domination and marks the end of any scientific enterprise on the soil of antique Rome, for eight centuries. Within one century the Romans lost all knowledge of the Greek language, which had been the language of science in the antique world, except for India whose influence on scientific world movements, therefore, was small in those days. Through this linguistic barrier the Western Roman Empire was completely cut off for the rest of its existence from any contact with contemporary scientific enterprise and remained without any influence upon it—a fact which is most noteworthy.

THE BYZANTINE EPISODE

One hundred and fifty years after Galen's death, a fellow countryman of his, *Oribasios* of Pergamon (+403), taught and toiled in Byzan-

tum, which in his life time quickly developed to be the cultural centre of the civilized world, destined to become the link between East and West. He laid down Galen's teaching and his own commentaries in 70 books, which proved of the greatest benefit for future generations, as he incorporated in this monumental work much of the best, achieved by the Greeks. Oribasios' compilation became so valuable because in his days a rioting mob of fanatic Christians burnt the Musaeon in Alexandria (391 A D), destroying a considerable part of the marvellous library which consisted of 700,000 manuscripts, including the complete Corpus Hippocraticum. In those days, more than one thousand years before the printing press was invented, when books could be reproduced only by handwriting, such a loss was irreparable and contributed in no small way to the decline of Alexandria which nevertheless persisted as a centre of learning, although not of research, for another 250 years up to the conquest by the Arabs in 641 A D. But the violent opposition of waning Christianity against the waning paganism was not the only reason for the fast decline of antique science on European soil.

SYRIAN AND PERSIAN INTERLUDE

In 431 A D, a purge of Byzantine Christendom started with banishing Nestorius, Patriarch of Jerusalem, for heresy, followed 50 years later, by a wholesale expulsion of all his followers. Among those emigrating Nestorian Christians were many Greek scientists and physicians who were hospitably received in Edessa, Nisibis and some other places in Syria, which had been a melting pot of ancient cultural currents for the last 1,500 years. Situated at the point of closest contact between Mesopotamia, Egypt and Judaea, dominated by Persians, Greeks and Romans in succession, a seat of old institutions of learning, it was an ideal place for the re-settlement of those learned refugees who did not wish for anything better than teaching their old cultural heritage in new surroundings. Some of the exiled Greeks felt threatened even in Syria and fled farther east, attracted to Jundi-Shapur in Persia, where in 350 A D a Sassanian king had founded a university. Now started a feverish activity of translating the Greek treasures into Syrian and Persian.

Between 500 and 680 A D, these Graeco-Syrian and Graeco-Persian schools formed practically the westernmost border of a fairly peaceful civilization. All the world west of it was in a violent upheaval due to invasions by successive waves of nomadic tribes. Ostrogothes and Visigothes, Vandals and Longobards overflowed the whole of Europe and North Africa, effacing for centuries almost every trace of Graeco-Roman civilization in this territory, although they were quite prepared to receive new seeds of learning. The absence of a common language between East and West was, perhaps, the main factor which throughout the Dark Ages prevented the re-awakening of the West and its re-integration into the world stream of thought. Latin intermingled with various barbarian idioms was spoken or at least understood all over the West but Latin literature, although rich in poetry and unsurpassed for the codification of law, was extremely poor in contributions to natural sciences and, especially, to medicine. It was particularly unlucky that the only encyclopaedic work, written in Latin and containing a vast amount of medical knowledge, that by Celsus,

remained unknown throughout this period and was rediscovered only in the 13th century

THE ARABS

Meanwhile, Greek science and literature had started its conquest of the Middle East, favoured by the unique feat of the Prophet Mohamed (570-632 A D), who in his life time succeeded not only in unifying the whole Arabic speaking world but also saw the beginning of the triumphal spreading of Islam beyond the original confines of Arabism. By 640 A D, Arabic rule over the Middle East was consolidated and in the following year Islam established a firm foothold in North Africa by taking Alexandria. Finally, in 711 A D, the Muslims, after their victory at Xeres de la Frontera (near Gibraltar), founded the Western Caliphate in Spain, a historical event of first magnitude. There, as everywhere under this new rule, a cultural blossoming set in, which had all the ripe flavour of the oldest civilizations on earth combined with a springly freshness, a directness and simplicity of approach which is found in the young, the nomadic newcomers in the circle of the cultured.

Without delay, the Arabs started translating Syrian, Persian and Greek works into Arabic which, apace with the military conquests of the Califs, soon became more of a world language than Latin was, and as much as Greek had been at the height of Greek domination. From Samarkand to the Indus, throughout the Middle East and all round the Mediterranean, Arabic was the common language. Some families made translating their profession for generations until, at the time when Baghdad was founded (762 A D), practically all the important writers of the past, such as Hippocrates and Aristotle, Galen, Onbasios and scores of others existed in beautifully made up Arabic manuscripts, saved by Greeks, Syrians and Arabs from loss and destruction by the barbarians, roaming Europe, secured of immortality as long as Arabic was understood. The Dark Ages with their incredibly complete destruction of all cultural achievements in art and literature, in science and political institutions, resemble the possibilities of the present atomic age in a fearful way, except for the very much greater difficulty to find a safe place for cultural treasures to-day.

But the Arabs were not satisfied with being custodians of a most precious heritage. Stimulated by the study of the past, they soon started on observations of their own. Their contributions to astronomy and chemistry, to algebra and to medicine are of greatest significance for the further development of science all over the world.

The early Califs of Baghdad were extremely broadminded, especially where medicine was concerned. They called Syrian Christians and Persian Zoroastrians as physicians to their court and we find among the medical advisers of Harun-al-Rashid the Indian *Mankha*, who translated Susruta's *Samhitā* and an Indian book on medicinal plants into Arabic. Hospitals were built and universities founded, where Persians, the oldest culture bearers of this area, exerted the strongest rejuvenating influence on the evolution of medicine. Imbued with all the knowledge of the past, Abu Bakr Mohamed ibn Zakariyya, called al Rhazi or *Rhazes* (+923), became the greatest single factor in promoting new medical knowledge in the Middle Ages. His observations on fevers, his differentiation between measles and small pox, his

monographs on diet and treatment remained text-books in the western medical schools upto the 16th century and represent classical treatises even to-day. Similar to Hippocrates, he took very little for granted and relied more on what he had observed himself than what was handed down from antiquity. He did not hesitate to oppose even Galen when his advice failed to satisfy him in practice. But what he found useful, he accepted, so he quotes Susruta and adopted his description of the various kinds of leeches. Through his and other Arabic writings, a considerable part of Indian experience, especially regarding herbs, was taken over by and freely used in Europe. Dozens of Rhazes' contemporaries, such as Ali Abbas and Isaac Judaeus, an Egyptian Jew, published their experiences which within one century had become so manifold and numerous that it required a genius of systematization to bring order into the amassed facts.

Just at the right time, when Arabic original research had reached its peak, such a man was given to the world in Ali ibn Sina, called *Avicenna* (+1037), a Persian, born near Bokhara. Never settling down at one place for a long time, he was devoted to poetry, to beauty, to science and to wine—a contemporary of Omar Khayyam, whose life his own resembles. Although he died at the early age of 58, his five books, called the *Qanun* or the *Canon of Medicine*, represent, perhaps, the most studied medical work in history, innumerable generations of medical students wrote their thesis on it, none could pass his examination without knowing every word of this standard work and for centuries every step in medical practice had to conform to it to be recognized as being in accordance with the rules of the art. Resembling Galen in the mastery of all that was known at that time, and in the perfection of his logical thinking, he surpassed him in the exactness of symptomatology and the completeness of dietary advice, results of Rhazes' preceding work. Although he did not add to the knowledge of anatomy and physiology, he was one of those universally gifted men who without effort brought an enormous amount of facts into a transparent system which convinced everybody and permitted apparently to deduce the solution of numerous problems, simply by applying intellectual effort, this way of thinking aroused a dangerous feeling of satisfaction, of knowing so much that it seemed unnecessary to turn to observing nature and to experimental research for finding answers to new questions.

Before concluding this short survey of the role the Arabs played in conserving and increasing medical experience, we have to mention *Abulqasim* (+1013), the only Arab who contributed considerably to and influenced the development of surgery. He was born in Cordoba in Spain, the capital of the Western Caliphate, then a city with over one million inhabitants, fifty hospitals and a university library which contained 200,000 volumes, his indications for surgical treatment, his methods and his instruments bear such close resemblance to Indian surgery that we may safely assume that Arabic surgery, as it was transmitted to Europe within the next century, contained considerable and significant Indian features, thus, the surgery of Salerno, Montpellier and Bologna, which crystallized from the twelfth century onwards, was as much descended from India as from the Arabs. The following century, the last of the great Arabic period, sees three interesting

personalities all of them physicians and philosophers, who exerted equally great influence in both of these capacities. The Muslim *Avenzoar* (+1162) and his friend *Averroes* (+1198), the great explorer of Aristotle and fearless freethinker, stirred western thought profoundly. Averroes was regarded with deep suspicion by the very sensitive Catholic Church which recognized to a wide extent Aristotle's authority but did not like those who roamed as free lances the realm of thought, to be called an Averroist in the 13th and 14th century dangerously attracted the Gestapo of those days. The third of these adventurous philosophers was the Jewish physician *Maimonides* (+1204), who had to leave Cordoba because he refused to embrace Islam. In those days, when Islam's splendour and power decreased, when the Christians in the West, the Tartars in the East knocked at the gates of the Arabic empires, Muslims became much less broadminded than they were as long as Mansur, Harun or Mamun adorned the throne of the Caliphs. Maimonides, however, found a second home in Egypt where Sultan Saladin appointed him his court physician, he wrote numerous medical books, of which some are still interesting, his philosophical writings try to reconcile Judaism with Aristotle, and philosophy with medicine.

EAST-WEST CONTACTS

Up to now, we have followed the way of eastern medicine amalgamated with Greek achievements to its refuge in Asia and back, along the African coast of the Mediterranean, to Spain, the Arabic part of Europe. Several times, already, we hinted at the influence of the Indo-Graeco-Arabic system of medicine, which represented the only scientific medicine of this era, on the development of medical thinking and working in Europe. In fact, Europe was not merely influenced, it was peacefully conquered by eastern wisdom which entered by two gate ways and was jubilantly received by an intellectually starved continent. From the South came a single man, *Constantine the African* (+1087), from the South West, somewhat later, the full stream of Arabic literature.

Constantine, born in Carthage in 1018, travelled far and wide in the Byzantine Empire, in Persia and India, and returned so heavily loaded with knowledge that he was viewed with suspicion. He escaped to Salerno on the southern coast of Italy where a sprinkling of Greek culture had remained, sufficient to maintain a receptive atmosphere. Here, according to a legend, four Masters, a Latin, a Greek, a Saracene and a Jew, had founded a medical school which had become known through a good surgeon, *Roger Frugardi*, whose pupils spread Salerno's fame. Of still greater interest are "the ladies of Salerno," of whom the best known was *Trotula* who flourished there at about 1050 A.D., she rediscovered a good deal of obstetric experiences, lost to the West and not further developed in the East since Soranus.

With the arrival of Constantine the reputation of Salerno grew with an amazing speed. He translated Greek and Arabic medical writings into Latin and so, for the first time after about 800 years, Hippocrates and Galen became known again to Europe, while Arabic medical literature, such as the works of Ali Abbas and Isaac the Jew, had never before reached European soil. Curiously enough, Rhazes and Avicenna were not among Constantine's gifts and were translated

about 100 years later by order of the Norman rulers of Salerno who held Arabic culture in high esteem Salerno, almost immediately, achieved the first rank among western centres of learning and from all over Europe pupils flocked there to acquire first hand knowledge of these unique treasures Constantine, who retired to the Benedictine monastery at Monte Cassino, was called *Magister Orientis et Occidentis* by the monks who revelled in his fame Although he had not added anything of his own to contemporary knowledge, it was due to him that the West came in touch again with the world stream of ancient and recent movements in medicine

The other port of entry of Arabic medicine and all that goes with it, was Montpellier, due to its fortunate position near the Spanish frontier In 1085, Toledo, one of the great cultural centres of Arabism, had been taken by the Christians and soon afterwards monks started the tremendous task of translating into Latin the vast Arabic literature found there Foremost among them was *Gerhard of Cremona*, soon called *Tholetanus*, who from 1170 A D onwards continued on a large scale what some Dominican monks had started in 1180 A D, to recover for the Western world the priceless jewels of Greek and Arabic scientific works by translating them into Latin

A WAKENING OF EUROPE

The first to be benefited by this miraculous opening up of inexhaustible wells of wisdom was Montpellier in southern France, then the centre of one of the oldest areas of Greek colonization, which had become the Roman *Narbonensis* ages ago It is significant that both, Salerno and Montpellier, from where Europe's re-awakening started, were situated on a soil, pervaded by Greek culture since the 6th and 7th century B C respectively, and in the closest neighbourhood of Arabic dominions, Spain here and Sicily there Both remained venerable institutions of learning, Montpellier up to this time, whereas Salerno was closed by Napoleon (1811) But none of the two produced the leaders of medical progress Montpellier was soon overtaken by Paris, whereas Salerno acted as a source of stimulation for the younger universities of Bologna and Padua For Salerno, Frederic II reserved the right of approbation of doctors of medicine and there was also fixed the curriculum of medical education which remained in force for several centuries Nobody could be enrolled as a medical student who had not studied "the Arts" for three years, so that only rigorously selected ones were admitted The reading of Greek and Arabic writers formed the main content of medical studies till high into the 16th century

But Salerno contributed also some work of her own to the revival of medical science, a pamphlet of four pages, the anatomy of the pig (*anatomia porci*) and a short manual for dissections awakened interest in acquiring more direct anatomical knowledge, a new trend which bore fruit first in Bologna Other famous works, produced by the combined efforts of the medical school of Salerno, were the "*Antidotarius*," a materia medica, and the "*Regimen Sanitatis Salernitanum*," written towards the end of the 11th century but printed and enlarged over and over again, in about 140 editions (Chevalier, 1944) till late in the 15th century It is a versified compendium of advice for keeping good health and treating diseases

Bologna was a university of quite a peculiar character (Castiglioni,

1945) The students were the masters and the professors their employees. The most surprising point is that this arrangement worked well and the medical school of Bologna attracted and produced men, second to none. There European surgery was founded, stimulated by *Abulqasim* (Abulcasis), but soon finding their own ways to mastership *William of Salicet* (+1277) based surgery on anatomical knowledge and raised the social standard of surgeons to approach that of physicians. He reintroduced the use of the knife which the Arabs almost had given up, preferring cautery. One of his pupils, *Lanfranc* (+1315), became a famous surgeon at the university of Paris, another one, *Mondeville* (+1320), brought anatomical drawings, copied in Bologna, and Salicet's surgical teaching to Montpellier, where at the same time an interesting man, the highly gifted, independent thinker *Arnaldo of Villanova* taught medicine. Arnold quarrelled with the Church, wrote classical treatises on divers medical subjects, dealt with women's diseases in his book on poisons because he regarded women as "venomous creatures," and died in 1311.

His contemporary in Bologna, *Taddeo Alderotti* (+1308), was a different man altogether. He united excellence as a typical scholastic thinker, with clear bed-side observation of clinical facts, published in his famous "Consilia." At the same university, shortly afterwards, *Mondino* wrote his "Anatomy" (1316), since Galen the first anatomical work which is based on actual dissections, though not yet independent enough to correct Galen's time honoured errors. His pupil *Guy de Chauliac*, one of the great French surgeons, carried Bologna's fame to the court of the Popes in Avignon.

Meanwhile, in 1222 a university had been founded in Padua and already one of her first teachers in medicine, *Pietro d' Abano* (+1315), a contemporary of Arnaldo and Alderotti, gave Padua great, but dangerous reputation. He had spent years in Constantinople to learn Greek with the aim of reading the classic Greek authors in the original. He pointed out serious mistakes of the Arab translators and also contributed considerably to the medical knowledge of his time. In the end, he was accused of heresy and only a timely natural death prevented him from being burnt on the stake.

RENAISSANCE

Bologna's zeal in reviving anatomy achieved great success in *Berengario da Carpi* (+1530), who discovered the appendix vermiformis, described the finer anatomy of the larynx, investigated tympanum and pineal gland, and was one of the first bourgeois collectors of great contemporary paintings.

Soon Padua overshadowed everything that had been done before in anatomical discovery and research. *Andreas Vesalius* (+1564), a student of Paris, at the age of 28, published the first volume of his immortal "*Fabrica de corpore humano*" (1543), achieving with one stroke complete independence of anatomy from the past, which had delayed progress since the times of Galen. His revolutionary work roused such an opposition in Padua that he fled to Spain where he was received with great honour by Charles V, whose medical adviser he became. Vesalius found an early death on a pilgrimage to the Holy Land.

Here, passing mention must be made of another revolutionary,

Paracelsus (+1541), a Swiss, who, after studying in Montpellier, Bologna and Padua, travelled all over Europe, from Spain and England to Russia and Turkey, taught in Bâle and died, at the age of 50, in Austria, a lonely, bitter man. He was a great genius and a hard fighter, whose life's aim was to make medicine independent of the old authors and to bring it back to nature, to unbiased experiment and observation.

Vesalius' contemporary in Rome was *Eustachius*, the author of a beautifully illustrated work on anatomy, which was lost for more than one century (published 1744). Among Vesalius' pupils are *Realdo Columbus* (+1599), who experimentally proved the pulmonary circulation, first described by *Michael Servetus* in Bologna, *Fallopian* (+1562), who described the Fallopian tubes and his "aqueduct," and *Fabricius ab Aquapendente*, who showed the best way for performing a tracheotomy and described the valves in veins.

XVII CENTURY MEDICINE

Fabricius' greatest claim to fame is that he was the teacher of *William Harvey* (1578-1657). Harvey graduated from Padua in 1602 and published his immortal discovery of the circulation of blood (*De Motu Cordis*) in 1628 (printed in Frankfurt), while he was Physician in Ordinary to King Charles I.

One of the greatest periods in the history of Bologna was the 17th century, when *Marcello Malpighi* (+1694) introduced microscopy into the study of anatomy. He first saw the capillaries, putting the final touch to Harvey's grandiose structure, he discovered the red blood cells and described the glomeruli in the kidney as well as Malpighi's bodies in the spleen, he investigated the histology of skin and liver and found that bile is secreted by the liver cells, and not by the gall bladder. He included in his studies the anatomy of plants and insects and achieved also here lasting results.

Malpighi's pupil and successor *A. M. Valsalva* (+1723) wrote an anatomy of the ear which remained the standard work on this subject for one century.

XVIII CENTURY MEDICINE

Valsalva's pupil *G. B. Morgagni* (1771) became the founder of modern pathological anatomy. For 56 years teaching in Padua, he was the first to correlate clinical findings with pathological processes, revealed by his masterly post mortem investigations, at the age of 79, he published his life work, the classical "*De Sedibus et Causis Morborum*" (1761), which contains the histories of 700 cases. He described for the first time the pathological appearance of pneumonia, cirrhosis of the liver, atherosclerosis, many different tumours and much else.

Morgagni's younger contemporary in the chair of anatomy in Bologna was *Lungi Galvani* (+1798), whose discovery of muscle contractions due to electric stimulation marks the beginning of experimental physiology of nerve and muscle, and led him to the invention of the Galvanic battery. His life work seems more important than that of many more brilliant scientists because due to it medicine became aware of the great possibilities for research, diagnosis and treatment, offered by the application of electric phenomena to medical problems. The use of those physical forces which culminates for the time being in

Roentgen rays and radio-isotopes represents one of the two essential differences between medical thought and medical work possible from the beginning of recorded history up to about 1650, and the facilities available after this date. There is no stinging reason why Vesalius' epoch-making discoveries should not have been made by the Alexandrian vivisectionists, some 1700 years before him, or why Harvey's revolutionary discovery of the circulation of blood should have escaped Galen, 1400 years earlier. But Malpighi's opening of a new world was not possible without the microscope, the invention of which, in its most primitive form, is due to the Dutch spectacle-maker Jansen in 1609, and the development of physiology during the 19th century with all its repercussions on clinical medicine and surgery is unthinkable without Galvani's fundamental observation and persistent investigation.

BEGINNING OF OXFORD, CAMBRIDGE AND LEYDEN

In these crowning developments, however, the old Italian Universities played a minor role because the political atmosphere in the Italy of the 19th century, which was fighting for unification and independence, was not favourable to scientific creative work. This was carried out at this time in Edinburgh, Paris and Vienna. Paris had been a centre of scientific life almost continuously since the 13th century although, off and on, religious quarrels and fights between the Church and secular powers threatened to rob it of its leading position. It was due to such events that English students left Paris in 1167 by order of Henry II and settled in Oxford, although studying of medicine was not permitted there for some time more. For this reason, we find British medical men teaching first in Salerno (Michael Scot, 1175) and later in Montpellier (Gilbert Angheus, 1250), before John of Gaddesden (1321), a graduate of Montpellier, transplanted regained medical science from the Continent to Meiton College in Oxford. Equally close ties existed between the Renaissance universities and Cambridge, where *John Caius* (1573), who studied in Padua in the days of Vesalius, revived medical teaching.

Edinburgh, among whose graduates we find men like Charles Bell, William Sharpey and Richard Bright, was one of the leading medical centres in the 19th century, it was here that J. Y. Simpson induced the first anaesthesia with chloroform (1847) and Lister taught his new doctrine of antiseptics. Edinburgh owes the foundation of the Royal College of Physicians (1681) as well as that of its medical school (1726) to Scotch students of the Dutch university in Leyden.

In Leyden, *Boerhaave* (+1771) was the admired teacher of thousands of pupils from all over the world. The origin of this school is interesting in several respects, it was founded by the Protestants in 1575 because of the intolerance towards non-Catholics growing at the Italian universities, such narrow-mindedness, however, was displayed by order of the Church authorities who imposed their counter-reformatory zeal on the Italian universities against their own will and so contributed to their decline.

The first medical teachers at Leyden, Schrevelius and van Heurne (+1601), were graduates of Padua, from where they brought the excellent method of clinical teaching at the bed-side, first practised by Alderotti in Bologna. This once revolutionary innovation was

developed to greatest perfection by Boerhaave, although never more than twelve beds were allotted to him

Vienna, finally, enjoyed the unfolding of the old Vienna School in the second half of the 18th century, when Boerhaave at the request of Empress Maria Theresa sent one of his most brilliant pupils, Van Swieten (+1772), from Leyden to Vienna to reorganize there medical teaching. That he achieved full success is proved by the galaxy of great men who in Vienna contributed so much to the spectacular progress of all branches of medicine throughout the 19th century

INDO-ARABIC CONTACTS

Closing the circle, we shall look once more to India, our point of departure. We mentioned already the close contacts between Indian and Arabic medicine. By the beginning of the 9th century A D, Susruta, Charaka, and Vagbhata had been translated into Arabic. Indian medicine, which for 3 to 4 millennia, from the days of the Indus Valley civilization up to those of Vagbhata, a contemporary of King Harsha, had made most important contributions to the medical knowledge of the whole civilized world, enjoyed a high reputation at the courts of the early Caliphs. *Mankha* was not only a physician at the famous hospital of Baghdad but was also credited with having cured Harun-al-Rashid (+809 A D) from a serious illness which the other court physicians failed to diagnose. This success maintained the traditional superiority of Hindu physicians over the local ones, established by *Salih*, who in the 7th century A D, competing with the Syrian Christian *Jurgis Bukht-Yishu*, chief physician to the hospital of Jundi-Shapur, succeeded in reviving a cousin of the Prophet (Hemmeter, 1 c). This high regard for Hindu medicine brought *al Biruni* to India where he lived from 1017 to 1030 A D and wrote a book on this country which remains one of the main sources of the history of this time. Somewhat later, *Chakrapani* (about 1100 A D) wrote his well known commentary on the *Samhitās* of Atreya-Charaka and Susruta, mainly a compilation of previous knowledge. Since then, or rather since Vagbhata, ceased further development of medicine in India. Vagbhata's significance for Indian medicine is similar to that of Aristotle for the Greek. His deep knowledge of all that went before him, his rich experience and clear mind enabled him to give a masterly picture of Hindu medicine at its best. He introduced mineral and chemical preparations into therapy. But if world medicine had stopped developing at this time, progress would have been arrested at the stage of the Alexandrian compilers, the last of whom, *Paul of Aegina* (+690 A D), a contemporary of Vagbhata, taught in Alexandria at the time of the Arabic conquest, and was held in high honour by the new masters. Medicine would have remained a highly developed craft without any resemblance to science. A code of elaborate rules would regulate the application of the 760 herbs, counted in the *Susruta Samhita* (Sudhoff, 1922), skilled craftsmen would handle Susruta's 101 blunt *yantras* and 20 sharp instruments (*sastras*) (Hemmeter, 1 c), and much valuable knowledge of eye diseases would have accumulated. But insight in the real working of the human system would be most vague and dim. Anatomy in India was derived from occasional glimpses on bodies, macerated by lying for days in water and not dissected but forced apart with grass brushes, the results of such crude methods, certainly, were remarkable in antiquity but are incomparably inferior

to scientific anatomy after Vesalius. The concepts underlying and guiding physiology and pathology are admirable speculations, much sound observation can be traced in the parts of the Samhitas devoted to those subjects. But how deeply do they differ from the facts, discovered during the last two or three centuries!

In the 16th century, we find Arabic medicine returning to its primary source, when Humayun resumed the throne in Delhi, he brought with him physicians from Persia where he had spent his years of exile. At Akbar's court we find 23 physicians of whom three were Hindus. The system of medicine practised there by the Persians was called Unani, a term derived from the word Ionian, the name of a Greek tribe which settled before 1000 B.C. in Asia Minor, used for all Greeks, in the East. At this time, preference was given to Persian physicians not so much for religious reasons, Akbar's tolerance being well known, but because of the actual professional efficiency of them based on their intimate knowledge of the Arabic medical classics who, as we have seen have incorporated in their teaching, in addition to their own work, all the experience of the Greeks, who in their turn had learnt all there was to learn from India, Persia and Egypt. A particular disadvantage of the Ayurvedic physicians as compared with the Persians was that they refused to perform blood letting which at the Mogul court was an essential part of therapy.

INDO-EUROPEAN CONTACTS

One of the first European physicians in India was the French *Bernier* (+1688), a graduate of the medical school of Montpellier, which centuries ago had been one of the first in Christian Europe to receive the wisdom of Graeco-Arabic medicine. Now, she paid back to the East her due of gratitude by sending her eminent pupil who endowed with all the knowledge of his time, including Harvey's discovery, served Aurangzeb for almost ten years. After his return to Paris, he published his delightful memoirs, one of the most important contributions to the history of the Mogul Empire in those days. Prior to him, during the rule of Jahangir and Shah-Jehan, the East India Company employed British medics in their settlements. Of some historical interest is *G. Broughton* (+1658), to whose professional skill the Company owed important privileges, granted by Shah Jehan. In the following centuries it was due mainly to the activities of medical men in the service of the East India Company and, later, to the members of the Indian Medical Service as well as to those Indian pioneers in the medical profession, who went to the United Kingdom for further studies that India was integrated in the current of world medicine which had one of its main sources in Ancient India.

Summary This very incomplete survey of the main stages in the development of medical science traces the development of Greek medical science to its eastern roots in Indian, Mesopotamian and Egyptian medicine, it follows its course westwards to Alexandria and Rome and eastwards again from Byzantium (Constantinople) to Syria, Persia and the Eastern Caliphate and back to the West with the Arabs to Spain. Then follows the providential and fateful reintegration of Europe into the progress of medical science by the penetration of Indo-Graeco-Arabic literature to Salerno and Montpellier, spreading speedily to Bologna, Paris, and Padua, the last of which deeply influenced

England Through Leyden (Holland), the tradition of Padua became the model of medical teaching in Edinburgh and Vienna. Finally, the circle is closed by the entry of Gracco-Arabic (Unani) medicine from Persia into India, followed by the import of XVII-century medical knowledge by French and British practitioners in the times of the later Moguls.

Concluding, it seems hardly open to doubt that scientific medicine is a single mighty stream nourished by many rivers, the sources of which are dimly traceable in remote antiquity. Nowadays, there is no room for the concept of a national medicine anywhere. The greatest periods in medical history have been those where no narrow-minded nationalism interfered with the freest exchange of ideas and experiences, such conditions existed during the 5th century B.C. in Greece, from about 750 to 1050 A.D. when the Arabs were world-conscious, and from the 12th to the 18th century, when all the European universities felt united in the supernational kingdom of seekers for truth.

As medical science equally assimilated all the contributions to knowledge from wherever they originated, no distinction is possible between eastern or western, indigenous or foreign medicine. The only existing difference is between ancient medicine, of which Ayurvedic medicine is a most interesting part and which should be studied from the medico-historical point of view, and modern medical science, which is one and indivisible, truly supernational.

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A STUDY OF THE IMMUNOLOGICAL EFFECTS OF LENS AND UVEAL PROTEINS

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An intraocular operation for the ophthalmologist is often a matter of despair. The greatest despair is when he sees the result of a particularly good operation getting wrecked under his very nose from a form of Iritis over which he has little control. I do not mean that mild Iritis that follows in the wake of every intraocular operation and has its nuisance value. I mean that severe form of Iritis against which no treatment can hold and ends in total loss of sight.

To get at the root of such disappointments has engaged the attention of many observers but one despairs the general tendency in such cases to attribute post-operative Iritis very light-heartedly to syphilis, mild sepsis, gout and rheumatism. Undoubtedly syphilis, tubercle and septic foci play a very important role in the causation of such an Iritis and many cases profit by instituting the right line of treatment based upon the correct causation factor. In spite of that there is a form of Uvitis that defies the usual treatment. When the usual line of treatment fails one is inclined to take cover under that vague term "rheumatism" where there never is any rheumatism and I plead guilty of such cowardice myself in my own practice. In justification of such an attitude one points to the beneficial effects of heroic doses of Soda Salicylas in such cases but this will undoubtedly relieve the pain of any painful condition in the body.

The study of the nature of such Iritis in our case is by no means new, though comparatively the literature is very thin, on this subject. The present day conception of this form of Uvitis is that it may be one of the following conditions:

- A Endophthalmitis phaco-anaphylactica,
- B Endophthalmitis Uveo-anaphylactica,
- both contributing to
- C Sympathetic Ophthalmia

In other words conditions A and B result from sensitisation of the uveal tissue of the eye from the presence of liberated lens and uveal matter respectively. That is lens and uveal proteins have antigenic properties and stimulate an allergic reaction within the operated eye.

Historical Landmarks In 1908, Uhlenhuth¹ found that lens protein is organ specific and lacks species specificity. That is the lens of all vertebrates behave similarly in immunology, so that the protein of say a sheep's lens will induce similar hypersensitising and immunising reactions in man as the protein of a human lens.

This piece of knowledge was utilised in trying² to explain the etiology of cataract formation on immunological grounds, and prevent its

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formation and even clear it by administering lens extract, but it failed. As a matter of fact it was demonstrated that the capsule of the lens is impermeable to globulins, the part of the serum that bears the antibodies.

Lagrange and Lacoste³ were the first to suggest that the lens-protein itself is a factor in post-operative intraocular inflammation. But they thought it was on account of the inherent toxicity of retained lens tissue which according to earlier observers acted as a good culture medium. This was the toxic theory and for that reason was called *Endophthalmitis phaco-genetica*. Not till 1922 was the term⁴ *Endophthalmitis phaco-anaphylactica* used for the first time by Verhoeff and Lamoine. They advanced their allergic theory and asserted that the delayed occurrence of Iritis after cataract operation or after a second needling in juvenile cataracts was due to hyper-sensitisation of the tissues of the eye and to some extent to the tissues of the whole body by the presence of liberated lens matters in the eye. As proof they pointed to the elicitation of skin-positive reaction to an intradermal injection of lens protein, in such individuals and the latent interval between the operation and the onset of symptoms.

Several observers and experimenters have taken up the threads of these rival theories, viz, toxic as against anaphylactic, to make their own observations and gradually the present concept has come into favour though not without a challenge, that the reaction is of an allergic nature. The greatest weight in support of this concept has been placed in recent years by the convincing experimental evidence of Woods and Burky⁵. Their team proved that the lens extract if prepared aseptically is not toxic in the normal individual, as believed by Gifford²⁰ and others, and the supposed inherent toxicity of the lens matter was mainly due to contamination. Also, in post-operative inflammation in subjects proved hyper-sensitive to lens protein, desensitisation with lens protein brings about an amelioration of the symptoms.

Burky⁸ in 1933 produced experimentally *Endophthalmitis phaco-anaphylactica* with lens protein through the intermediary of bacterial toxins and so the subsequent studies in this direction have been with lens protein activated by bacterial toxins.

Similarly Elsehng¹⁰ and Woods,¹⁰ Nakamura¹⁰ and others have shown that Uveal pigment is also organ specific, lacks species specificity and can act like a foreign protein just like lens protein. So Elsehng put forward the allergic theory of sympathetic ophthalmia. According to it injury to the exciting eye results in absorption of Uveal pigment which sensitises the pigmented tissues of the whole body and particularly of the homologous organ, namely the opposite eye. Further absorption of this Uveal pigment results in an allergic reaction of the sensitised uveal tissues of the opposite eye, which we call sympathetic ophthalmia.

Arnold De Veer¹¹ has stressed the role of lens-protein allergy in the causation of *sympathetic ophthalmia*.

Again now a group of cases have been reported by Woods and Little¹² where an endophthalmitis followed injury to Uveal tissue only. The onset here was also delayed, the opposite eye remained unaffected and the histological picture of enucleated eyes showed epitheloid and giant cells as in endophthalmitis phaco anaphylactica and sympathetic ophthalmia. So it may be termed *Endophthalmitis Uveo-anaphylactica*^{13,14}

With a view to ascertain the truth of these theories for ourselves we undertook a study of the immunological effects of these two proteins, and I assure you we have found the study very fascinating. The chief difficulty was to prepare the necessary extracts which with great patience and care we were able to prepare for ourselves. Moreover, at the time when we were planning on this work, we had an unusual flooding of clinical material needed for our observations. Some of them were inflammations of our own manufacture and others not of our own, and if our figures today sound a little alarming to one who has the prospect of facing a cataract operation on himself, I may relieve his mental distress by stating that these observations coincided with an unprecedented frequency of unpleasant complications.

Preparation of Materials In our present study we have not made use of activated lens and uveal proteins for diagnosis as well as for therapeutics. Although, it is expected that the activated materials would give better results, yet the simple lens extract and uveal tissue suspension have been employed for the following reasons:

- 1 It is proposed to investigate these clinical conditions with activated materials in a subsequent study.

- 2 A preliminary study with simple materials is essential for correct relative evaluation.

- 3 The additional factor may not only be the staphylococci. It may well be streptococci and more probably tuberculococci, or it may be some constitutional disequilibrium e.g. rheumatic or gouty attacks.

- 4 All these additional factors may be tested for separately, if one chooses to test their combined action with the two proteins under trial.

Preparation of Lens Extract The method employed here is that given by Woods and Burky^{5, 15}. Briefly the crystalline lenses of bovine eyes, fresh from the slaughter house are extracted intracapsular. The capsule is opened while the lens is still pushing into the corneal incision. The lens matter is collected in a flask containing broken glass and lens solvent which is N/100 Ammonium hydroxide solution. It is shaken for 24 hours and then kept in a refrigerator for one week. Later it is passed twice through centrifuge. The clear extract is then filtered through Seitz Filter. Next, the percentage of the lens matter is determined and then with the addition of Saline and water necessary standard dilutions are prepared. All this is to be done by observing the greatest aseptic precautions, and a preservative like Cresol has to be added. It is to be kept in a refrigerator as otherwise at room temperature it gets opaque.

Preparation of Uveal Pigment and Uveal Tissue Suspension The method employed by us was a modification of one described by Hugo Lucia¹⁶ for preparation of uveal tissue toxin.

Uveal tissue is removed from bovine eyes and kept in separate test-tubes containing normal saline. These are kept in a refrigerator for about a week and then each sample is tested for sterility. The contaminated ones are discarded and the contents of sterile ones are pooled together in a flask containing broken glass and shaken continuously for 18 hours. Then the whole stuff is macerated in a glass mortar with glass beads and then filtered through gauze. Sterility test is again done. Now percentage concentration is determined and desired dilutions are prepared. We usually keep the following dilutions:

| | | |
|------|-----------|---------------------------------|
| Lens | 1 in 50, | 1 in 100 for therapy |
| | 1 in 100, | 1 in 200, 1 in 1000 for testing |
| Uvea | 1 in 100, | 1 in 200 for therapy |
| | 1 in 100, | 1 in 500, 1 in 1000 for testing |

For control of bovine serum sterile dilutions of 1 in 100, 1 in 500, 1 in 1000 are required. These materials are always kept in a refrigerator.

Test for Hypersensitivity There are 2 methods of testing 17 allergy. In the present study this method was not employed. It is proposed to do it in subsequent studies, so as to ascertain the relative usefulness of both tests and also ascertain the relation between cutaneous and serological reactions.

(2) Intracutaneous test that again may be 1 Clinical

The intracutaneous test is made by injecting intradermally 0.1 c.c. of 1:100 lens extract or 0.1 c.c. of 1:200 Uveal pigment suspension, according to the allergen for which the patient is to be tested. We use a tuberculin syringe with a fine needle for the purpose, and inject intradermally in the skin of the flexor surface of the forearm four fingers below the bend of the elbow, left forearm for lens and right forearm for uvea. The test is read 24, 48 and 72 hours after the injection. Within 5-15 minutes of injection the skin reacts as in food allergy by the production of a wheel with or without erythema. This passes off quickly and is not of clinical value.

If the reaction is to be positive we get a delayed tuberculin type of reaction which consists of a wheel with erythema and induration. This appears in twelve hours and then begins to fade.

Interpretation of this clinical test is by no means easy. Specially, in the beginning for evident reasons, such as the condition of the skin, its pigmentation and sensitivity to other beef allergens. This latter can be excluded by doing a control with bovine serum.

Standardisation of this test can be done in two ways — (1) By observing the degree of erythema and induration it produces, empirically recording with a number of +es as we do in the Wassermann's Test etc. (2) By minimum dilution of the allergen required to cause a visible skin reaction.

Histological Cutaneous Test Friedenwald¹⁸ conceived the idea of histological examination of the excised piece of skin at the site of injection. A positive reaction shows typical histology of sympathetic ophthalmia at the end of two weeks. In our present study we have not employed it as a routine test, but we have here a slide to show the reaction in one of our cases. However, we have learnt to read this histological test clinically. In a normal person if a small quantity of the Uveal pigment is injected intradermally, the pigment remains as a visible tattoo mark at the site of injection. In a uveal sensitive subject this pigment disappears very rapidly within two or three days, leaving no trace of the pigment behind. This is in unison with the histological change in uveal allergy where the pigment is phagocytosed out by epitheloid and giant cells. This, however, applies only to the uveal pigment and not the lens protein.

Our study extends over 161 eyes of 146 patients operated by us and five cases operated elsewhere. These five cases are not included in the

tables here but we shall mention about them later as they offer important points for study

TABLE I

| Operation | Group I Cut Sens. 0 Inflam 0 | Group II Cut Sens 0 Inflam + | Group III Cut Sens + Inflam 0 | Group IV Cut Sens + Inflam + | TOTAL |
|-------------------------|------------------------------------|------------------------------------|-------------------------------------|------------------------------------|-------|
| Extracap Cat Ext. | 00 | 10 | 11 | 21 = 10% | 132 |
| Intracap Cat Ext. | 21 | 1 | 1 | 2 = 8% | 25 |
| Trephining | | | | 2 | 2 |
| Iridectomy for Glaucoma | | | | 2 | 2 |
| | | | | | 161 |

In the above table, in trephining and iridectomy cases we cannot offer the incidence ratio because only the eyes which had post-operative inflammation were treated for cutaneous sensitivity

The comparative lower figure for intracapsular cases is in keeping with our experience, that intracapsular extractions give rise to a more benign post-operative course

TABLE II

| | Total Tested | Positive to LENS No of cases | Percentage | Developed No of Cases | IRITIS Percentage |
|------------------------|-----------------|---------------------------------|------------|--------------------------|----------------------|
| Lemolne & Macdonald 19 | 108 | 14 | 8.0% | 7 | 50% |
| Gifford 20 | 86 | 11 | 12.0% | 6 | 50% |
| Our Study | 157 | 35 | 22.3% | 10 | 54.3% |

A comparative table showing the incidence of +ve lens cutaneous reaction after cataract operation, and the incidence of a stormy post-operative course in such lens sensitive subjects

Our figures show a higher percentage incidence of +ve reactions and a higher percentage incidence of stormy post-operative courses in such lens sensitive subjects than the American observers. But as I have already stated for some inexplicable reason we were flooded with such stormy cases during the period of our observations that our general experience is not in keeping with the figures arrived at. Another study of this nature will certainly deserve our attention.

TABLE III
AN ANALYSIS OF GROUP II CASES IN TABLE I

| TOTAL | DIABETES | IMPROVED WITH TUBERCULIN | DELAYED CLOSURE OF WOUND | SEPSIS |
|-------|----------|--------------------------------|--------------------------------|--------|
| 11 | 1 | 5 | 1 | 3 |

We can understand in these cases the cause of the post-operative inflammation in absence of lens hypersensitivity. Out of the three cases of sepsis two eye-balls were saved with penicillin and sulfonamide therapy and one case was lost because of the extremely low general condition. This compares favourably with the incidence of sepsis in the presence of lens hypersensitivity (see Table IV) where one eye was lost in spite of treatment, and one saved with lens desensitisation along with penicillin and sulfonamides.

TABLE IV
AN ANALYSIS OF GROUP III IN TABLE I

| TOTAL | DESENSITISATION DONE BEFORE OPERATION | DESENSITISATION NOT DONE BEFORE OPERATION |
|-------|---------------------------------------|---|
| 12 | 7 | 5 <div> { 1 intracapsular ext. 3 mildly lens +ve 1 strongly lens +ve </div> |

This explains why inflammation did not take place although one would expect such an event with a demonstrable hypersensitiveness to lens protein, except in one case where the lens sensitivity was strongly +ve.

Also due to the disturbed city conditions in Bombay, it may be that some of them were unable to report, because these post operative inflammations may take place as late as two months after the operation.

TABLE V
AN ANALYSIS OF GROUP IV IN TABLE I

| Total | Late Iritis Controlled by Desens | Uveonaphyl Controlled by Uveal Pigment | Haem | Sepsis | Detach | Late Iritis Uncontrolled by Desens | Sympathetic ophthalmia |
|-------|----------------------------------|--|------|--------|--------|------------------------------------|------------------------|
| 23 | 11 | 1 | 1 | 3 | 1 | 5 | 2 |

Out of twenty-three cases of Group IV, in eleven the clinical story was more or less the same,—operation on one eye, little or no inflammation. Then operation on the second eye on an average later than three weeks—rather severe post-operative inflammation setting in later than the 7th day after operation. When tested for sensitivity found to be all +ve. In these cases desensitisation brought about a successful end result eventually.

Typical of this group though a little different from it was Gaspar Norris—a Christian aged sixty four. Simple extracapsular operation performed on 12-6-46. Post operative course uneventful until reported on 25-6-46, that is 12 days after the operation, with pain in the eye. Routine treatment gave no relief. Tested on 8-7-46 negative to lens 1/100 but on 10-7-46, +ve to lens 1/50. Desensitisation started on 12-7-46, and brought to full dose of 2 c c. Final vision was 6/12 with glasses. He was operated on the other eye on 7-10-46. An intracapsular was attempted in view of his existing lens hypersensitivity, but the capsule burst, a little vitreous escaped, and much of the cortex remained behind. Desensitisation was continued and post operative course was uneventful. This is a sure instance glorifying the therapeutic value of desensitisation, because ordinarily one would have expected to get a severe iritis in the second eye operated.

Comments and Conclusion The problem of deciding whether the three conditions, endophthalmitis phaco-anaphylactica and sympathetic ophthalmia are allergic conditions or otherwise has been approached from the clinical side only, and the amount of clinical material analysed, we believe is sufficient testimony to decide it more in favour of an allergic nature of this condition. Sensitisation is a variable process, and the rapidity with which sensitisation and desensitisation takes place depends on the kind of allergens. Some allergens are active, some are very poor. The poorer ones act slowly and take a longer time to manifest their presence and lens and uveal pigment, in their relatively pure form, that is unactivated, are poor ones, the uveal tissue being poorer so than the lens. Hence the relative infrequency of endophthalmitis uveo-anaphylactica (only one case in our series) in comparison with endophthalmitis phaco-anaphylactica. Also iritis in that one case took place twenty-eight days after the operation. However both lens and uveal proteins may be activated by bacterial toxins as proved conclusively by Burky, because the hitherto impossible production of endophthalmitis phaco-anaphylactica in animals was rendered possible by him by this means. So we get severity of a variable nature and incidence of iritis at a variable interval after the operation in different cases. Where the homologous eye is rapidly sensitised because of a previous extracapsular operation on the opposite side, the incidences have been relatively severe and quicker.

The effect of desensitisation we feel, has been definitely proved, though such treatment is still open to criticism that it may be acting like a non-specific protein. It is practically impossible to tell whether an observed improvement is due to the desensitising or vaccinating effect of the injections, to the non-specific proteins reaction or the normal recuperative power of the patient. Who can tell?

As regards dosage of desensitisation the poorer the allergen, the larger the dose required. In the beginning, with our knowledge of dosage for tuberculin injections, which is my weakness, we did not go all out with the dosage for desensitising. Soon we had to drop our timidity in this direction, and an eye was narrowly saved from enucleation by a timely stepping up of the dose.

As regards activation of the lens and uveal proteins there may be several kinds of activation—a bacterial toxin, notably we feel the tuberculo-toxin, non-bacterial toxins, e.g. the activation of lens protein by pigment protein and vice-versa, or the simple influence of trauma and general resistance. For that reason we feel that a fairly clear idea of the probable nature of such ocular reactions may be expressed vividly in the form of a fraction

$$\begin{aligned}
 & \text{Lens allergy} \times \text{activating factor} \\
 \text{A Phaco-anaphylactic reaction} &= \frac{\text{Resistance of patient} \times \text{lens immuni-}}{\text{ty}} + \text{trauma} \\
 & \text{Pigment allergy} \times \text{activating factor} \\
 \text{B Uveo naphylactic reaction} &= \frac{\text{Resistance of patient} \times \text{Pigment}}{\text{immunity}} + \text{trauma}
 \end{aligned}$$

Sympathetic Ophthalmia = A, B or (A + B) in the opposite eye

Against the theory of allergy it is stated that if that is the case then there is no sense in removing the exciting eye when the fellow eye is already sensitised to the lens and uveal proteins and that any insult to the sound eye months or years later will provide that shock which will precipitate sympathising inflammation in the injured eye. In answer to that we have three very good cases.

Mr Chinoy was operated for cataract on 1-12-42 R E. The operation was particularly successful. On 2-12-43 he came with Iritis in the left eye, a very mild affair, but which kept on getting worse and worse in spite of all the treatment and consultations. Eventually the eye was enucleated on 1-5-44, and a section report said that it presented a histological picture of sympathetic ophthalmia. Since this case came under our observations long before we ever thought of this subject, we have no data of his cutaneous sensitivity to lens, neither have I the slide to show you the section. All this time the sympathising inflammation was taking place, there was no inflammation at all of the operated eye. As a matter of fact on 15-6-44, one and a half months after the enucleation of the sympathising eye the vision in the operated eye was with +11 +1 Cyl horizontal = 6/9. It shows the probable presence of lens and/or uveal sensitivity in the unoperated eye which got precipitated a year later from some unknown cause. Incidentally it gave lie to the statement that for sympathising inflammation to take place there must be activation of inflammation in the exciting eye.

The second case was of a sympathetic ophthalmia not of our manufacture. We found her to be lens and uveal positive. We tried to desensitise her, but I must confess the desensitisation was not done too vigorously and not at regular intervals. She showed considerable improvement in the sympathising eye. However, before we undertook the operation on the sympathising eye, we advised enucleation of the previously operated eye playing for safety. A month after the enucleation, I removed the cataract in the fellow eye. A perfect intracapsular. My hope of restoring useful vision gradually faded as her eye got from bad to worse and she pays a regular visit to the K E M Hospital to drive home the fact about the futility of doing an enucleation, once uveal or lens sensitivity is established in the fellow eye.

Case III Mrs Parekh, a Parsee lady of 68 years, was operated on the R E for cataract extracapsularly on 8-6-45. There was some iris prolapse which was excised on the 4th day after the operation. She was discharged on the seventh day with a red eye, slightly painful and watering. Routine post-operative treatment with a Soda Salicylas (grs 60 per day) mixture was advised. Within three weeks of the operation her eye condition had improved sufficiently to enable her to return to her native place—Navsari. About two months after the operation she got pain in the operated eye, and was told she was getting glaucoma. About a week later she complained of failing vision in the opposite eye, and, she was told she was getting glaucoma in the unoperated eye as well. She came to Bombay on 9-8-45, was readmitted. She presented a picture of a fully developed sympathetic ophthalmia, the exciting eye much worse than the sympathising eye. Carbachol Eye drops locally, large doses of Soda Salicylas internally, tuberculin and milk injections were administered and she rapidly showed improvement for a while, the K P's got less, tension was reduced and she was comfortable. But

she ceased to show further improvement. We decided to enucleate the operated eye where the vision was only perception of light. The other treatment was also continued. The condition of her unoperated eye improved very slowly and in another two months' time we thought her left eye was saved.

She once again returned to Bombay on 8-8-46 for further diminution of vision in the left eye. There were no K.P.'s, the tension was normal. The vision was finger counting at two feet only, which was due to the progressing cataract. We decided to operate, and so we tested her for lens and uveal hyper-sensitivity. She was definitely positive to lens but not to uvea. We gave her a course of lens desensitising injections, and operated on her left eye for cataract on 26-12-46. A combined intracapsular operation was done. She made an uneventful recovery on the whole. However, her vision could not be improved beyond 6/60, because of the vitreous opacities and an atrophic nerve, probably as an after effect of the sympathetic inflammation. To one fact I specially wish to draw attention, that after the operation she has developed slightly higher intraocular tension which is very persistent, though it is being kept under control with eserine.

Case I suggests that after that operation, hypersensitivity most probably to lens only got established in which the homologous eye shared. Almost exactly a year later, sympathising inflammation started in the unoperated eye, by some unknown precipitating factor, probably a mild trauma, and so the supposedly hypersensitised eye was not proof against an insult to it a year later.

The difference between case II and III is that in II lens desensitisation was not done properly, whereas in III it was done prior to operation on the second eye. In II the second operation ended in total blindness, in III the eye-ball was saved, proving the futility of enucleation and the value of desensitisation after established sympathetic ophthalmia. The removal of the exciting eye, only removed the fodder that feeds the flame of allergic reaction in the fellow eye, but the fire smoulders in the unoperated eye which you dare not touch without proper desensitisation.

Our study of these cases drives us to side with the view of Woods in explaining the probable nature of these inflammations that development of lens and/or pigment allergy apparently alters the biologic defence mechanism of the operated eye, in condition A and B and of the fellow eye in sympathetic ophthalmia in such a manner that the sensitised eye gets easily subjected to other noxious agents.

A study of this subject is not only of academic interest but has yielded lessons of great practical value.

1 We have learnt the value of desensitisation with specific allergens.

2 An intracapsular operation is preferable to extracapsular in these cases where lens hypersensitivity is established as after an extracapsular operation on the first eye.

4 We feel that we can now intelligently and not empirically meet the post-operative complications with greater calm and equanimity.

As you will see we have entered our cases in a specially prepared

case book This has been printed after our preliminary experiences, and so large gaps are present in the filling of these

Our future study will be infinitely more elaborate and critical and complete with the histo-pathological and experimental evidence wherever possible

It opens for us newer problems in the light of the existing theory and experiences We hope to stand before you with a further study of similar cases, though I pray that the incidence of such inflammation may not be as high as in this paper, but just natural

(I have to thank Dr Dhurandhar my colleague for the use of his cases and active co-operation, Drs Bhende and Monteliro of the pathology and bio chemical departments, and all of my assistants for their interest and keenness to help)

Dr Dhavagude May I ask Dr Cooper whether it is possible to put the allergens into the eye and test the local hypersensitivity rather than the general hypersensitivity by injection into the skin, and if so would it not be preferable?

Dr Dhurandhar May I ask Dr Cooper how he can explain the presence of lens hypersensitivity and post-operative inflammation after intracapsular operations?

Dr Oak May I suggest that while collecting the full data for this work, the patient's general resistance should be taken into account, because in our hospital practice we find that although the patients are not well nourished, their general resistance to infections of all kinds is good

Secondly the sex must be noted, for my impression is that sympathetic inflammation is more common in females

Finally it is my experience that when cataract operation is performed on both the eyes at the same time, the post operative course is particularly uneventful May I ask for Dr Cooper's remarks on the same question

Dr J K Mehta Is it not a fact that sympathetic inflammation after suppuration is very rare? If so, can Dr Cooper explain the same on immunological grounds

Dr Cooper in reply said Dr Dhavagude's suggestion to put a drop of the allergen in the eye for testing the hypersensitivity of the eye, as we do with other allergens is useful, but I feel that the lens and uveal proteins are such poor allergens in their pure state that they may not cause any reaction of diagnostic value in the eye If they do, then the chances of getting a severe ocular inflammation are high

To Dr Dhurandhar I can reply that the incidence of iritis with lens hypersensitivity in intracapsular operation, however, is very small Sometimes when we do remove a lens intracapsularly a little bit of the lens matter may be left behind if the capsule bursts at the last moment In such cases it is possible for hypersensitivity to develop as happened in one of my cases recently The cataract was removed intracapsular but the eye persisted in being red and inflamed An iris prolapse had also developed which was cut A little bit of the iris still remained in the wound and about a month later he developed secondary glaucoma Day before yesterday I tested him for lens and uveal hypersensitivity and did a paracentesis at the same time When the aqueous escaped I noticed a thin thread like substance in the wound I picked it out with forceps and removed it It looked like a thin shred of lens capsule Evidently it was left there after the intracapsular operation Only this morning when I saw the cutaneous reaction, he seemed to be mildly positive to lens I believe such an incident can explain what Dr Dhurandhar wants to know

Dr Oak has made a number of suggestions We have not recorded the general resistance, in all cases, but where complications have occurred, we have noted the general condition of the patient, and have incorporated the same in the fraction by which we finally express the severity of the reactions in endophthalmitis phaco and uveo-enophthalmitis

As regards the higher incidence of sympathetic ophthalmia in females, I have no knowledge

Finally his suggestion of doing a cataract operation in both the eyes at the same time is in keeping with our own experience We have been doing this lately ourselves whenever an opportunity arises Formerly we used to dread doing the operation on both the eyes together for fear of sepsis, but with the advent of sulfonamides and Penicillin we were tempted to operate on both the eyes at the same time Our small experience tallies with Dr Oak's observation, that on the whole the post-operative course is uneventful in such cases Our experience however, is far too limited to dogmatise on it

Dr J K Mehta wants an explanation on immunological grounds of the fact that sympathetic ophthalmia is rare after suppuration of the injured eye. The only way I can explain Dr Mehta's question, is that suppuration destroys in some way or the other the antigenic property of lens and uveal proteins.

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Critical Notes and Abstracts

PAIN, NEUROMUSCULAR, USE OF VITAMINS E AND C IN TREATMENT OF, (J R Williams, New York State J Med Vol 47, pages 1125-1126, May 15, 1947) In view of the reports that muscular pain of long standing may be due to deficiency of vitamin E and the general reduction of oil-soluble vitamins in the blood plasma of chronically ill persons, these vitamins were administered to 35 subjects. Patients were (1) diabetic or (2) nondiabetic with persistent pains in the extremities, (3) persons with diabetes and osteoarthritis, and (4) nondiabetics with arthritis and Heberden nodes. At breakfast each patient received the minimal daily requirement of vitamins A, D, C and B. At noon each received 25 mg of vitamin E and 50 mg of vitamin C, and at supper, 40 mg of natural mixed tocopherols. Treatment was continued daily for from one month to a year or more. A number of patients in each group obtained complete or partial relief from pain through this treatment. In some carefully controlled cases, relief was reported to be dramatic and sustained, in others relief was partial, although positive, suggesting the possible need for larger doses.

Reflections and Aphorisms

MEDICAL COMPETENCE

"Medical care consists of *knowledge*, applied by men to patients. This knowledge is the working capital of medicine, built up through centuries of experience and decades of research. We often proudly refer to modern medical knowledge as of "huge extent" or "staggering proportions," and relative to the accumulated facts of a century ago, this is true. Yet in any given area, knowledge is not so massive that it cannot be encompassed by the human intellect. Knowledge simplifies as it progresses, and multiple ill understood theories are swept away by the strong currents of new basic facts. Each significant advance in medicine renders obsolete a multitude of former writings or practices. There is nothing overpowering in the amount of our present knowledge, but the application of this knowledge to sick human beings is a complex and difficult affair that requires the use of the second medical resource, *men*. Without men who can apply it properly, medical knowledge is sterile. Unfortunately, a medical degree confers neither wisdom nor honesty on the recipient, wisdom in its broader sense includes not only factual knowledge but also the ability to apply knowledge with judgment and mercy. Honesty is the *sine qua non* of medicine, without which medical practice degenerates into the collection of the fee without the contribution of commensurate benefit.

In addition to the wise and honest doctor-scientists, we have our full share of loud-mouthed snap diagnosticians, and researchers who are long on theory but short on judgment are as numerous as surgeons whose concern for the patient fades if convalescence is stormy.

For all their effectiveness, modern medical techniques are dangerous and medical knowledge is of little avail unless applied by men of wisdom and integrity. Modern tools enforce on us the necessity of becoming better draftsmen. When medical care was simple and ineffective it was also harmless, and the fine exercise of judgment required of the present day physician, working with his sharp and penetrating weapons, was less frequently required. Yet the raw material from which physicians are fashioned has not changed since the early days of medicine.

Is there any way of increasing the total number of effectives? Better recruiting should be the answer. The admission committees of medical schools must raise their standards by every honest means. The interest and enthusiasm of the most capable undergraduates in the colleges must be aroused. The breed must be improved, even if it requires artificial insemination!"

—Ed. *New Eng J Med* 1947

"If there is an unenviable reputation in the medical profession it is that of the chronic scribbler in the journals or of the chronic babbler in the societies."

—William Henry Welch

"I do not believe in considering the results of experiments on animals as proven facts in human pathology, as is too often done, but rather guides to clinical and pathological observations."

—William Henry Welch

"I hope I have learned from Prof. Ludwig's precept and practice that most important lesson for every man of science, not to be satisfied with loose thinking and half proofs, not to speculate and theorize but to observe closely and carefully facts."

—William Henry Welch

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Original Contributions

TUBERCULOSIS OF THE SKIN

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Tuberculosis of the skin is of comparatively rare occurrence in this country, though one occasionally comes across cases of various types of this disease. So different is the clinical picture in these different types, that it is difficult to believe that the same organism is responsible in each case.

The course of the disease, depends upon the soil in which it has been planted. Reaction will be different in a patient who has never had this disease before and in one whose skin, through previous infection, has become sensitised or allergic.

Other factors affecting the course of the disease are the virulence and the number of the organisms present, the presence or absence of anti-bodies and their amount, and the natural resistance of the patient. Another factor of importance, is the age of the patient. Progressive forms of the disease and also those types which develop after one of the specific fevers, like multiple lupus, are common in children, immunity in whom has not developed to any great extent. In fact, the different clinical entities have little in common except a common etiology.

Some of the manifestations are localised in type and are produced by the introduction of fresh organisms from an outside source. These are examples of exogenous infection. On the other hand in endogenous infection the organisms are already present in the body at some focus and are conveyed to the skin through the blood stream.

As an example of the different course the disease takes in two cases of exogenous infection, one might mention primary inoculation tuberculosis which almost exclusively occurs in young children who have not acquired any degree of immunity. It is characterised by a well developed reaction, which includes a lymphangitis, and enlargement of lymph glands draining the area, in much the same way as the primary chancre of syphilis and is frequently termed a tuberculous chancre. Fever is usually present. On the other hand, inoculation tuberculosis in an adult who is rendered more or less immune to the disease will show no general reaction but a mild and purely local one at the site of infection, which develops a warty appearance.

The tubercle bacillus is responsible by its local action for all forms of skin tuberculosis. In some forms such as Lupus Vulgaris, Tuber-

culosis Verrucosa Cutis, Primary Tuberculous Complex, they occur in varying numbers in the lesions and animal inoculation of these tissues is usually successful. On the other hand in the hematogenous types such as the tuberculides and the sarcoids, the bacillus is present only in the very earliest stages and has disappeared or much diminished in numbers by the time the disease has developed.

The degree of reaction to various dilutions of old tuberculin varies in the different types of tuberculosis *e.g.* where allergy is strongly developed, such as in Lupus Vulgaris, Scrofuloderma and in Lupus Verrucosa Cutis, high dilutions will give a positive reaction. Other cases such as the Tuberculides, give only a moderate reaction. Sarcoids usually give a negative reaction to tuberculin even in low dilutions.

Ethology As I have already remarked, the tubercle bacillus is responsible for the different varieties of skin tuberculosis. The human type of bacillus infection occurs in most cases, the bovine type in a few and it is thought that the avian type of infection very rarely occurs. Tuberculoderma is much more commonly seen in northern European clinics and whereas one might see one or two cases in an out-patient clinic in two or three months in this country, in London or Edinburgh or Copenhagen some cases will come up almost daily. The disease is much more common in children and young adults, although its ravages, especially in Lupus Vulgaris, may be encountered in older people who have actually acquired it in earlier life. Sometimes the development of natural immunity may arrest further progress of the disease.

Skin tuberculosis is more common amongst the poor, with a low standard of nourishment and hygiene, which brings in its wake a poor body resistance. Naturally it occurs more commonly where opportunity for transmission exists *e.g.* where a family member is suffering from active pulmonary tuberculosis. A child, or even an adult, in such circumstances is liable to inoculate his skin by scratching. Cases of Lupus Vulgaris following vaccination have been reported. Tattooing is frequently followed by a verrucous or warty type of tuberculosis in the adult. Verruca Necrogenica or post-mortem wart as it is frequently called, occurs in certain professions *e.g.* people dealing with dead bodies such as those employed in post-mortem rooms or anatomy departments, or in persons who look after patients with visceral or pulmonary tuberculosis, such as attendants in a sanatorium, who may accidentally inoculate themselves with infected material. These are probably examples of inoculation with the human type of bacillus. On the other hand Tuberculosis Verrucosa Cutis, which frequently occurs in bare footed agriculturists, butchers, etc., leads to a surmise that the bovine type of bacillus is responsible.

Lupus Vulgaris may be produced not only by inoculation, but may spread to the skin by the lymphatics or through the blood stream. In disseminated or multiple Lupus, which usually follows an attack of measles, the bacilli from some focus are carried by the blood stream to various parts of the skin. In scrofuloderma, on the other hand, spread of the bacilli is by direct extension from some underlying focus such as bone or gland. Tuberculosis Cutis Orificialis is usually secondary to visceral tuberculosis, and tuberculous ulcers at the anus occur in subjects with visceral or pulmonary tuberculosis.

Classification A certain amount of confusion in nomenclature has been caused by various descriptive terms being used to describe one clinical entity. The terminology I have used is suggested by Jadassohn. The best classification is that suggested by Gans who divides skin tuberculosis into two large groups (a) Localised tuberculosis and (b) Hematogenous Types

LOCALISED TUBERCULOSIS OF THE SKIN

1 LUPUS VULGARIS

I have already mentioned that this is essentially a disease beginning in childhood. The primary lesion of Lupus is a minute, pin-head sized, soft, reddish brown, semi-translucent tubercle or nodule, located in the corium. Several nodules join together and form patches. Most frequently they appear on the face about the nose, and spread to the cheeks. They may protrude slightly above the skin, or be flush with it. Pressure on the nodule with a dioscope or thick strip of glass, will reveal a yellow or brown area which from its resemblance to "apple jelly," is called "an apple-jelly nodule."

Subjective symptoms are usually absent and the extension of the disease is slow. Scaling, may or may not be a feature. The patch extends peripherally, and scar formation occurs at the centre. The scar in an old patch is parchment like and slightly depressed. The disease may run a varied course, there being three main types viz the atrophic, the hypertrophic and the ulcerative.

In the *atrophic type*, a smooth scar occurs as healing takes place and scattered apple jelly nodules are to be seen chiefly at the periphery, a few remaining behind. In the *hypertrophic type*, the surface of the growth is warty and sometimes a slight exudate, which may be purulent, is present. In the *ulcerative type*, the ulcers have an irregular border, the base is deep seated and dirty, blood supply is poor and healing slow. Secondary infection, with pus formation, crusting and tenderness of the part are usually to be found.

I have already remarked that the initial nodules appear about the nose, and here the alae nasi and the soft cartilage are destroyed, leading to the deformity known as "beak nose." The lobe of the ear is frequently destroyed by this disease and when it occurs about the eyes, it gives rise to the condition called ectropion. The lips may be reduced to narrow slits, preventing speech and proper nourishment.

On the body, Lupus shows a less destructive tendency, and appears to be more widely spread. A favourite place is on the buttocks, where the bacillus probably is inoculated into the skin as the result of a child sitting on tuberculous sputum. The disease heals at the centre and extends at the edge where active nodules are always to be seen. The central scar usually contains a few dormant nodules, which are a frequent focus for recrudescence of the disease. The border is polycyclic or serpiginous and shows a tendency to become verrucous.

The mucous membranes are frequently attacked, particularly that of the nose, and it is possible that in many cases, the disease may originate here. The mucous membrane of the lips, the gums, the palate, the buccal mucosa or the tongue may be affected. Here, owing to the moisture and warmth of the part, and infection by secondary organisms, the lesions may show a warty growth or may ulcerate. Extension of the disease is usually slow.

There is one type of this disease called *multiple disseminated Lupus Vulgaris*, occurring usually in children after measles. This is quite often seen, the skin being affected simultaneously on various parts of the body. The patches vary in size and consist of small, discrete nodules or areas as large as a rupee or even larger. The patches consist of a collection of nodules sometimes scaly and sometimes warty. Otherwise the appearance is the same as that of Lupus occurring on the face. A rare form of disseminated lupus occurs more frequently in adults. It is called *Lupus Miliaris Disseminatus Faciei*, and affects chiefly the face as an eruption of discrete nodules, apple jelly in appearance and pin-head to split-pea in size. The eruption comes on rapidly and involutes after a varying interval. There are more clinical varieties of Lupus Vulgaris, described in literature, but these are rarely seen and do not merit mention.

Complications of Lupus Vulgaris An associated eruption of different type may occur concurrently with Lupus Vulgaris e.g. Scrofuloderma and Tuberculous Ulcers. Tuberculosis of bone and joint may also be present. Pulmonary tuberculosis as also Visceral tuberculosis may also follow. Carcinoma is also a rare complication.

Pathology This is typical of tuberculous infection and shows an infiltration in the corium with epithelioid cells, small round cells, plasma cells, giant cells and almost invariably the tubercle bacilli.

Prognosis In early cases this is good, and restricted areas can be completely destroyed. But where the disease has spread to large areas of skin, local treatment is difficult and the patient finds it a great trial to collaborate with his physician. In very early cases, on a not too prominent or unexposed area, complete surgical excision of the diseased portion is the best treatment, but if a few nodules are left out, the disease is sure to relapse, spontaneous cure being most unusual.

Course The course of this disease is most erratic and varies in different individuals. In some, there are long periods of inactivity. In others, the disease spreads slowly. Old nodules in the centre of the patch or at its periphery suddenly develop activity. Destruction follows in its wake leading to the deformities such as ectropion, etc. which I have already referred to.

Differential Diagnosis In a typical case, the diagnosis is fairly apparent. The youth of the patient, the location of the disease, the slow spread, the typical apple jelly nodules, or the verrucous appearance, all favour a diagnosis of Lupus Vulgaris. Syphilis may sometimes simulate this disease. The ulcerating nodular syphilide, bears some resemblance to it, but it occurs in older people, spreads very much more rapidly and is completely peripheral in its extension, no nodules being contained in the scar as in Lupus. Other signs of syphilis will also be present, and the W R should be positive. Syphilis also attacks bone rather than cartilage, and the nasal bones, if involved, will show destruction whereas the cartilage escapes. The history of a sore, generalised skin eruptions in the past, mucous patches, joint pains, the typical multiple adenitis, syphilitic alopecia and in women a history of abortions or still births, will favour a diagnosis of syphilis. Should an adult have Lupus he will probably give a history that it commenced in childhood. Lupus will remain in one place, but syphilis will heal at one spot and appear on a completely different one.



Fig 1 —Extensive scarring following Lupus Vulgaris in a young boy



Fig 2 —Lupus Vulgus of several years duration in a young girl. This is a case which was probably infected by sitting on tuberculous sputum



Fig 3—Lupus Verrucosus Cutis in an adult following inoculation of the foot
This is probably a case of infection by the box type of bacillus
Fig 4—Lupus Verrucosus Cutis following infestation on the forearm

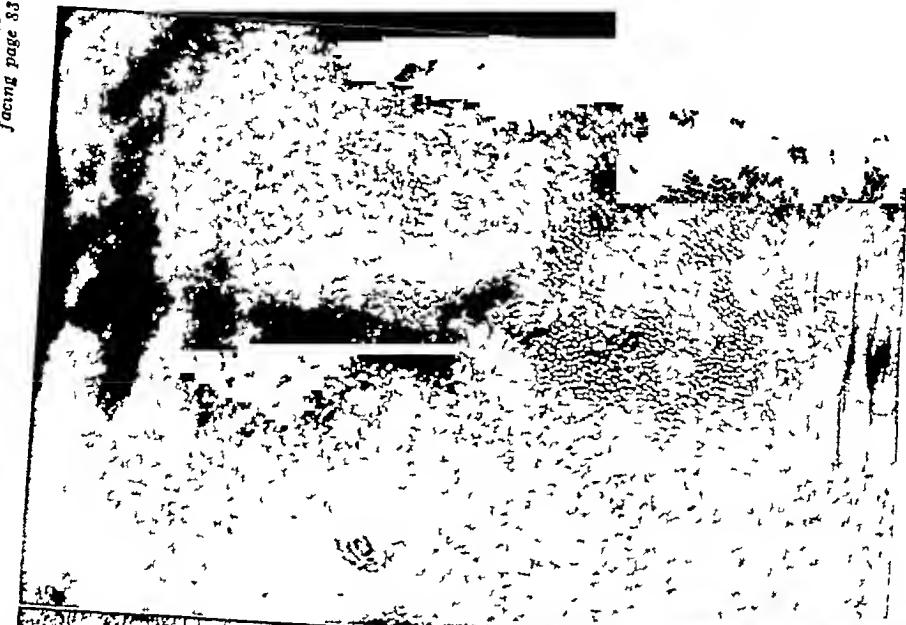


Fig 4—Lupus Verrucosus Cutis in a boy had a large mass of
cervical glands tubercular in origin

Lupus Verrucosus may resemble *Psoriasis* but in *psoriasis*, the scales are typically dry and silvery and when scraped away they reveal the membrane of Duncan Bulkley, which when removed reveals the typical bleeding points. *Psoriasis* too has a peculiar distribution, appearing chiefly on the extensors (knee, elbows, sacrum and scalp) and it is probable that some lesions in these locations will assist in the diagnosis. *Psoriasis* has a habit of appearing and disappearing periodically, although in some cases a patch may persist for years. Scar formation never occurs. Lupus on the other hand is invariably persistent. Scars will be present where healing has taken place. A search for apple jelly nodules should be made in the case of Lupus.

Lupus Erythematosus This disease, occurring as it does on the face, enters into the differential diagnosis. The distribution is typical. The cheeks and the bridge of the nose, the ears and the scalp are affected. Central scarring is also present. Scaling will be present, with typical projections on the under surface of the scales. The mouths of the pilosebaceous follicles will be found to be dilated. *Lupus Erythematosus* occurs later in life than *Lupus Vulgaris*. The spreading edge of the lesion is raised but not nodular, and there are no ulcers or crusts.

In a long standing case of Lupus, and quite frequently those that have been treated with X-rays over a long period, *epithelioma* of the skin may develop, and a biopsy will be of help.

Treatment—General Treatment is mainly that of tuberculous patients in general. An abundance of vitamins especially A and D, hypophosphites and other tonic preparations containing iron and arsenic are often useful. Lomholt treats his patient with a diet abundant in vitamins A, B, C and E in cases of extensive Lupus in debilitated patients. At the Finsen Institute the diet is supplemented with 50 grammes of butter and two carrots, two tablespoons of wheat germ and the juice of one lemon. This contains the above mentioned vitamins. Opinion on the restriction of sodium chloride is divided. A change of air, if possible to a hill station, is to be recommended. Exercise and an out-door life should be encouraged.

Local Treatment An isolated nodule or small patch, if seen early, should be surgically removed, but this is not practicable in most cases where the face is involved, because of the resulting scar.

The Finsen Light treatment has always given good results and is very popular in Europe. More recently Lomholt, who is in charge of the Finsen Institute, has devised an improvement on the lamp. Briefly, Ultra-Violet rays produced by a carbon-arc are passed through a series of water cooled filters. The applicator, which is of various shapes and sizes according to the part to be treated, rests against the skin. Only a small area is treated at each sitting. The weight of the lamp on the skin is adjusted to cause a diminished flow of blood, in the part to be treated, and an exposure of the rays for about one hour is given at a sitting. A severe reaction is caused at the site, a blister resulting. After a short time this heals and leaves a fine scar. The lamp however is expensive and not in common use.

Ultra-Violet ray baths are a useful adjunct in the treatment of *Lupus Vulgaris*. X-rays are not so frequently given because they have to be given over a long period, and new growth frequently results.

However in experienced hands they give quick relief but the scar frequently shows telangiectasia

Chemical selective caustics have long been used. Liquid acid nitrate of mercury used as a paint, and pyrogallie acid in 10% strength in an ointment base, are the two favourites. Although they do have a selective action on lupus tissue, they result in rather a painful response from the surrounding tissues as well, and require a lot of determination on the part of the patient and persuasion on the part of the physician, if used over a period of time. In this hospital we have generally used potassium permanganate, ground into a powder. The affected part is scarified with a sharp knife until all diseased tissue is thoroughly opened up, and the powdered permanganate is rubbed into the part and this is covered with sterile gauze. After 24 hours the gauze is changed. Within a week healing takes place and a fine scar is left. Isolated nodules which may have escaped treatment may then be destroyed with trichloroacetic acid.

Some dermatologists have used tuberculin ointment of about 5% strength, with a certain measure of success. Norman Walker speaks highly of this method, but it has never gained wide use. Tuberculin injections have also given good results in some hands but they should be used with great caution.

Gold injections have given good results also. Chaulmoogra oil injected intra-dermally into the nodules also has its advocates.

The most recent advance in therapy has been the treatment of Lupus Vulgaris with *Calciferol*¹. Charpy in France and Thomas and Dowling² in England, reported their findings in a number of cases of tuberculosis cutis with the administration of vitamin D₂ or Calciferol. As early as 1930, experimental tuberculosis in rabbits had benefited from large doses of irradiated ergosterol. It was observed that under the influence of this substance, tuberculous tissue tended to become calcified.

Charpy gave his vitamin D₂ in an alcoholic base. Calcium was given along with the vitamin, of which 600,000 I U was administered three times a week for three months and then once a week for a further three to six months. In 39 cases of Lupus reported, all were cured although some (27) were given local treatment as well.

Dowling and Thomas gave 38 patients with Lupus, 50,000 I U three times a day. A course of treatment lasted two months. This was followed by a period of rest and was then resumed again. The serum calcium was found to be considerably raised and gradually returned to normal after one to three months.

Renal disease and arterio-sclerosis are contraindications to therapy with calciferol, large doses sometimes causing injury to the kidney and aorta. Various side effects have been reported. Over-dosage according to Bills³ may cause "nausea and loss of appetite, vomiting, cramps, diarrhoea and frequent urination, occasionally neuralgia along the course of the mandibular nerve, tenderness of the gums and teeth, muscular and articular pains, dizziness, muscular weakness, headache, haziness of memory and numbness and tingling of the extremities". These symptoms are an index of tolerance to vitamin D₂. The effect of the vitamin is increased by giving calcium and phosphorus with it. Exposure to ultra-violet light also has a similar effect.

Symptoms of intolerance disappear if the drug is withheld

We have treated six cases of Lupus Vulgaris at the K E M Hospital. Unfortunately only one case took the drug for more than two months, the others defaulting at earlier periods. They are only mentioned because they showed no signs of intolerance to calciferol, during the period of its administration. The preparation used was High Potency Osteln tablets each containing 50,000 I U, and kindly supplied by Glaxo Labs. The one case who is still under treatment, has been admitted and observed for a period of five months. On admission she showed patches of multiple Lupus on the face, arm and leg. One patch on the arm showed changes of a warty nature (Lupus Verrucosus). She has received three tablets (150,000 I U) daily without a break, and has improved remarkably. The serum calcium has shown no tendency to increase from the normal, and she was given, quite latterly, generalised ultra-violet baths. The nodules have tended to subside, three ulcerative lesions have completely healed up, and ectropion which was present to a remarkable degree, is much less obvious. No local treatment was given, except a zinc cream.

The warty growths on her arm have almost completely flattened out, and the patient has suffered from no toxic effects. Calciferol therapy because of its ease of administration, and the distinct benefits it confers, is a decided advance in the treatment of cutaneous tuberculosis. Material in this country is scanty, and we will have to rely on experience from clinics in countries where the disease is more prevalent.

Promizole,⁴ a synthetic sulphone drug, has been tried and although successfully used in infected guinea pigs has not been found of much use clinically. Headache, nausea and gastric discomfort were common and Leucopenia and generalised toxic erythema occurred in some cases. *Streptomycin* however, has given better results and American workers are optimistic that the new and more purified preparations will give less toxic symptoms. The drug is of most use where a heavy infection of tubercle bacillus is present and less helpful, but worthy of a trial in skin tuberculosis, especially with the tuberculides.

2 PRIMARY COMPLEX OF TUBERCULOSIS (Tuberculous Chancre)

This is a rare type of skin affection, and occurs chiefly in children, or those adults who have never developed any immunity to tuberculosis as a result of prior infection. It is an exogenous infection. The tuberculin reaction becomes positive after infection. Locally an ulcer occurs. There is a lymphangitis and the lymphatic glands draining the area become enlarged, tender, and may go on to the formation of a cold abscess. There is usually some fever present.

Etiology Some injury to the skin, provides an entry for the tubercle bacillus *e.g.* contact with infected sputum.

Treatment Surgical excision may be useful in certain cases. Tuberculin injections may be used in selected cases. Localised and generalised ultra-violet therapy should be given and X-rays to the affected part may assist in cure.

3 TUBERCULOSIS VERRUCOSA CUTIS (Verruca necrogenica)

This occurs in people who either have or at some time have had, tuberculosis, without clinical evidence, and whose resistance to the germ is well developed. It is also an exogenous infection and a form of inoculation tuberculosis and occurs chiefly in (1) people dealing with

tuberculous bodies *e g* pathologists, medical students, anatomists, etc (2) people dealing with infected animals such as veterinary surgeons and butchers (3) from infected sputum in patients who themselves are suffering from active pulmonary tuberculosis

Diagnosis As a rule the disease occurs on the fingers or hands, for obvious reasons. A warty growth or crusted lesion on a slightly reddened background with a violaceous halo. Sometimes a little pus may exude from the lesion. The profession of the patient may help in the diagnosis. The prognosis is good. Many cases undergo spontaneous involution.

Treatment Surgical excision is the best method of treatment, otherwise the lesion may be destroyed by the electro-cautery or any of the methods suggested under Lupus Vulgaris. General treatment is the same as for Lupus Vulgaris.

4 TUBERCULOSIS CUTIS ORIFICIALIS

This is a form of ulceration occurring in tuberculous people with low vitality. Actually it is an extension of the disease from an inner active focus *e g* it occurs on the tongue or lip in people with active pulmonary tuberculosis or at the anus in patients with intestinal tuberculosis, and on the genital organs in patients with tuberculosis of the kidney or bladder.

Diagnosis One or more tubercles coalesce to form a nodule which later ulcerates to form one or more ulcers showing weak granulations. The lesions are situated in the corium, are soft and have irregular edges. The prognosis is always bad, as these patients suffer from advanced tuberculosis.

Treatment, includes the general treatment of tuberculosis. Attention should be given to the primary focus and the local lesion may be destroyed by electro-cautery. X-ray irradiation has also given good results.

5 SCROFULODERMA (Tuberculosis Colliquativa)

This occurs in people as a direct extension from an underlying focus in lymph glands or bones or joints. The glands of the neck are most frequently involved. The skin shows a nodular infiltration, and assumes gradually a dusky red colour. With extension of the disease the skin becomes thin and atrophic and the surface breaks down and ulcerates discharging a sero-purulent material. Frequently sinuses are formed. Healing is slow, with characteristic scar formation.

Diagnosis The disease is common in children and young adults. The location of the disease, the age of the patient, the typical ulceration, all lead to a straight-forward diagnosis in most cases. The tuberculin test will be positive.

Treatment is that of the underlying lesion and is mainly surgical. General treatment is the same as for Lupus Vulgaris. Locally ultra-violet rays, especially to the larger lesions are distinctly beneficial.

HAEMATOGENOUS TYPES

The group of diseases described under this heading, comprises those in which the patient has a primary focus of tuberculosis either in the lung or glands or bone and whose skin becomes allergic to the bacillus and its toxins. Under certain conditions, the bacilli are disseminated in the blood stream and reach the allergic skin and where they occur in

large numbers, an eruption results. This eruption is modified by the degree of allergy or anergy (absence of allergy) present in the skin and varies in different individuals *e g* where allergy is very marked the tuberculides occur. On the other hand allergy is mildly developed or absent, in the case of Sarcoids.

1 ACUTE MILIARY TUBERCULOSIS This disease usually occurs after measles and more rarely, whooping cough. A symmetrical and generalised eruption of small, brownish red, nodules sometimes grouped together, occurs. Ulceration takes place in course of time and crusts form over the ulcers, which may contain a few miliary nodules. Tubercle bacilli are found in large numbers. There is a generalised disturbance, with toxæmia and fever and usually evidences of tuberculosis in the other systems is present and the issue is fatal, in most cases from tuberculous meningitis.

Treatment is ineffectual, and palliative measures should be resorted to.

2 PAPULO-NECROTIC TUBERCULIDE This eruption occurs on the face, about the elbows, and on the extensor surfaces of the arms and forearms, and on the buttocks and the legs. Typically, it begins as a crop of tiny papules which undergo central necrosis and heal with the formation of a pitted scar.

The papule is painless, a dull red, firm in consistency and indolent. The eruption shows various stages of involution, as fresh crops keep coming out.

Treatment General treatment is that of tuberculosis. Ultra-violet irradiation is useful. Many cases recover spontaneously but the eruption is liable to recur as long as the tuberculous focus is present. Gold or Bismuth injections have given good results, as also tuberculin in some cases.

3 LUPUS MILIARIS DISSEMINATUS FACIEI This is a symmetrical follicular eruption affecting chiefly the face and neck. The papules are purplish or yellowish in colour and occur in groups. Pressure with the dioscope, as used in Lupus Vulgaris will show typical apple-jelly nodules. The papules show no tendency to ulcerate, and on the face, occur about the lips, the nostrils and on the cheeks. Crops of papules come out at intervals, over a period of months and when eventually healing takes place, fine scars are left behind.

Treatment The eruption may disappear spontaneously and local treatment is not called for in most cases. Besides the general treatment of tuberculosis, ultra-violet irradiation and injections of gold or N A B usually give good results.

4 ROSACEA-LIKE TUBERCULIDE, so called because of its resemblance to Rosacea, occurs on the forehead, chin, the cheeks and ears, as an eruption of smooth, flat, sometimes crusted, slightly elevated papules. In colour they are red or brownish red. Diascopic pressure reveals an apple-jelly nodule. Symptoms are absent, but in some cases a tuberculous history or a pulmonary focus of the disease may be present. The tuberculin reaction is positive and a histological examination may be necessary in a doubtful case.

Treatment is very much the same as in the other tuberculides, gold injections, bismuth injections and in some cases tuberculin therapy. Ultra-violet irradiation in moderate doses also does good.

5 LICHEN SCROFULOSORUM This type of tuberculide occurs most frequently in children or young adults who have a focus of infection. The skin is in a highly allergic state and the tuberculin test is strongly positive. The eruption is a grouped follicular one occurring in small round or oval patches on the flanks and front of the trunk. Each papule may have a horny spine or small scale at its apex. In colour they are brown, red, or may be the normal colour of the skin. The affected part has a typical goose-skin appearance. The histological picture is that of tuberculosis.

Treatment is in general that of tuberculosis. If a focus is present it should be eradicated if possible. Locally, one or two per cent salicylic acid in equal parts of cod liver oil and vaseline may be rubbed into the affected sites. Ultra-violet rays should be given.

6 ERYTHEMA INDURATUM OF BAZIN This disease occurs chiefly during the winter months in cold countries. It affects chiefly in young females, with a history of lung or gland tuberculosis. Its location is on the lower third of the backs of the legs, and is symmetrical. At first, small round or oval nodules may be felt under the skin and gradually they protrude above the skin surface. They increase in size very slowly, break down and ulcerate. The ulcers are irregular in outline, painless and after some months, heal leaving depressed, pigmented scars. New lesions frequently appear.

Differential Diagnosis is chiefly from the gumma of syphilis. A history and other evidences of syphilis are absent in Bazin's disease. The age of the patient may help, as syphilis usually occurs in older people, is symmetrical, and the W R will be positive.

Erythema Nodosum occurs on the fronts of the legs usually and covers a shorter period of time during its evolution. The nodules are red, more painful and inflamed, and ulceration does not occur.

Varicose Ulcers occur in older people of both sexes, are usually single and frequently asymmetrical. Varicose veins are always present.

Prognosis The disease is erratic in its course, and frequently new lesions tend to come out as the older ones heal.

Treatment is that of tuberculosis in general. The patient should be kept in bed and the circulation in the legs should be improved. An elasto-plast bandage applied to the part, as in varicose veins, is of help. Gold injections have been reported to give good results. Ultra-violet rays both locally and generalised, assist recovery.

7 SARCOIDOSIS This is a systemic disease involving besides the skin and nasal mucosa, other structures such as the bones, the lungs, the kidneys, the liver, etc. The eruption is polymorphous in character.

Clinical description The rash, which may be localised or generalised, shows characteristically a tendency to progress, with frequent intervals of remission and relapse. Ulceration does not occur. There are two main types, a superficial or Boeck type and a subcutaneous or Darier-Roussy type.

Sarcoid of Boeck In this variety the lesion may be a small or large nodule, or infiltrated plaque, firm to the feel and sharply circumscribed, occurring on the face, the back or the limbs. In colour it may be brown or purplish. The surface is smooth and very little elevated. Spontaneous involution may take place with scar formation and atrophy. Ulceration is a rare occurrence.

Sarcoid of Darier-Roussy In this type the nodules form in the sub cutaneous tissues They develop slowly and are painless They are round or oval and elastic They appear more frequently on the trunk, and vary in size They are very rare In colour the skin may show no change or may be a dull red or purple Sometimes the lesions become annular, with depigmented, slightly atrophic centres where involution takes place whilst the disease extends at the edges Other tissues may be involved as already mentioned Tuberculin tests are negative and animal inoculation is also negative

Diagnosis Biopsy shows circumscribed miliary tubercles either in the superficial or deep parts of the corium, according to the type of sarcoid Sarcoids must be differentiated from syphilis, in which other symptoms and signs will be present such as generalised adenitis, joint pains, a history of exposure and of previous skin eruptions and a positive W R In tuberculoid leprosy the clinical and histological pictures are very similar, but sensations will be altered in the case of leprosy

Prognosis is good except in cases with visceral involvement The disease runs an erratic course with periods of remission and relapse

Treatment in general is that of tuberculosis Gold, bismuth and arsenic all have their advocates and pyro-therapy is reported to have given good results X-rays to the part are highly spoken of

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STERNAL PUNCTURE AND MALARIA

by

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History As long as 1903, Pianese obtained marrow for examination by trephining the femur, Ghedians in 1908, removed some from tibia by similar means. This procedure in the hands of Zadek gave valuable information on the histology of pernicious anaemia. The disadvantages of this method were (1) that it was not possible to repeat this operation many times in the same patient and (2) that the red marrow is confined to small areas at the upper ends of long bones. In diseases, wherein there is excessive demand for cells, the whole medullary cavity may contain bone marrow e.g. in advanced leukaemias and severe pernicious anaemias. In these cases, valuable information could be obtained by tibial trephining, but in agranulocytosis, only fatty tissue will be obtained by the above procedure. Obviously, therefore, it is better to obtain specimen from a bone that always contains active marrow e.g. from sternum. Seyfarth in 1923 realised the advantages of obtaining sternal marrow but he did so by trephining sternum—the procedure which cannot be undertaken lightly. The modern method is that of sternal puncture, which was first performed on small children by Caronia in 1922 and by Arinkin on adults in 1929. It is a very convenient method of obtaining human marrow during life, and it can, if necessary be performed several times on the same patient. It is described as one of the most modern of the techniques included under the term 'Clinical Pathology'.

Uses—Ever since the introduction of this procedure by Arinkin, sternal puncture has been very widely used. Most of the punctures reported in the literature have been made for the detailed scientific study of, diseases of haemopoietic system. There are a number of conditions, in which the diagnosis can be arrived at solely by means of sternal puncture e.g. acute leukaemias or aleukaemic leukaemias, etc. Sternal puncture is very useful in the following conditions —

- Acute and chronic leukaemias
- Leukaemoid reactions
- Various types of anaemias
- Gaucher's disease
- Thrombocytopenic purpura
- Agranulocytosis
- Kala azar and malaria
- Glandular fever—to exclude acute leukaemias
- Marrow culture in cases of suspected enteric
- For saline infusions or blood transfusions, particularly in children and obese persons

A sternal puncture needle should be thick and strong. A movable guard on the needle itself is useful in order to avoid the danger admittedly slight of penetrating the bone too deeply. The needle designed by Witt fulfils every requirement and is quite convenient for use, though in the absence of such a needle a stout lumbar puncture needle can serve satisfactorily.

A paper read before 73rd meeting of Sheth G S Medical College and K E M Hospital Staff Society on 9.8.47 with Dr. N. D. Patel in the chair.

Method of doing sternal puncture—Sternal puncture is done most conveniently in the centre of sternum at the level of second interspace. Patient lies flat without a pillow and hair over the upper half of sternum is shaved off. Skin is cleaned with spirit and painted with iodine. It is anaesthetised with 1 to 2 cc of one per cent novocaine upto the subperiosteal tissue. Sternal puncture needle is inserted vertically through skin, subcutaneous tissue to bone and firmly pressed through cortex with to and fro rotating movements the upper end resting on the xiphoid eminence and needle being steadied by the index finger. As soon as we penetrate marrow, the resistance decreases. No dependence should be placed on sound or feel when the bone is pierced as in some punctures, there is no indication that the medullary cavity has been reached, i.e. so called 'give' may be absent. When the needle is firmly fixed on the sternum, the stylet is removed, syringe is attached to the needle and aspiration is attempted. If no marrow fluid appears, stylet is replaced, needle is advanced a little further and aspiration is tried again. This is continued until marrow fluid appears in the syringe. This is often accompanied by painful sensation in chest, evidently the result of producing a negative pressure in the marrow cavity. 0.1 cc to 0.2 cc of marrow fluid is withdrawn.

In the present study sternal puncture was done on 175 cases. Most of the cases selected for the study complained of fever with rigours. Since pyelitis is a very common cause of fever with rigor in females, male subjects were selected for the study in order to obviate the necessity of examining urine. 174 cases were males and only one was a female. Out of this 175 cases, 105 cases were taken up from the outpatient department and the remaining 70 cases were admitted in the K. E. M. Hospital with some complaints, which required hospitalisation. The cases from the outpatient department were taken to the ward, sternal punctures were done and patients were sent home subsequently. Most of them were apyrexial when sternal punctures were done. Films were made directly from the marrow fluid and stained with diluted Giemsa solution. Films were prepared at the same time from peripheral blood. Long and tedious search was made of both peripheral and sternal smears to find out malarial parasites. No extra cellular forms were recognised as diagnostic. The results are given below—

| | Total No | Parasites present | Both sternal & peripheral | Sternal alone positive |
|-------------|-------------|----------------------|---------------------------------|------------------------------|
| O P D cases | 105 | 35 | 27 | 8 |
| Indoor " | 70 | 48 | 37 | 11 |
| Total | 175 | 83 | 64 | 19 |

In the 11 indoor cases of sternal alone positive, the following types of parasites were seen

| | |
|---------|-----------------------|
| 4 cases | —Crescents |
| 4 " | —M T rings |
| 1 case | —Crescent & M T rings |
| 2 cases | —B T rings |

In 8 outdoor cases with sternal puncture alone positive

| | |
|---------|--------------------------------|
| 4 cases | had crescents |
| 2 " | had M T rings |
| 2 " | had B T rings and trophozoites |

Thus out of 19 cases of sternal puncture alone positive, 15 cases were of *pl falciparum* and 4 cases were of *pl vivax*, as shown below

| | |
|----------------------------|------------------------------------|
| 8 Crescents | } 15 cases of <i>pl falciparum</i> |
| 1 Crescent and M T ring | |
| 6 M T rings | |
| 2 B T rings & trophozoites | } 4 cases of <i>pl vivax</i> |
| 2 B T rings | |

All the above cases, where sternal alone was positive were cases with varying symptoms like neurasthenia, low fever, dysenteric like symptoms, pulmonary consolidation or subnormal temperature and a collapsed state. In two cases quinine were already administered for about 18 hours before the smears were taken. Sternal punctures were done in most of cases because of the palpable spleen. These are some of the conditions in which sternal smears are useful for the diagnosis of malaria.

In the present study of 175 cases, 88 cases were parasite positive. 64 cases out of these 88 cases could be diagnosed from peripheral smear alone if prolonged and repeated search were made for the parasites since in 4 cases blood smear was taken 2 to 8 times to get the parasites whereas sternal smear was positive even during apyrexial period. In the sternal smears, the parasites were seen often within a few minutes whereas in some of the peripheral smears, it was with great difficulty and after a prolonged search that parasites were found. Most of the pyrexial malarial cases can be diagnosed by examination of peripheral smear but sternal puncture offers a supplementary way of diagnosing those cases where sporulation is so scanty that peripheral blood parasites seem to be absent.

In an unselected series of 294 cases of malaria treated by Rumbell et al, 256 cases were diagnosed from peripheral blood examination only. The remaining 38 cases revealed the parasites only by sternal puncture. Of the latter cases, many were so atypical as to have obtained such provisional diagnosis as neurasthenia, affective disorders and sandfly fever.

SOME OBSERVATIONS ON THE CASES

In the present series of 175 cases, in addition to fever with rigor, other clinical manifestations in some of these cases were, Palpable spleen, abdominal pain, enlarged liver, pulmonary manifestations, diarrhoea, herpes labialis and unconscious state as shown in the following table.

| Clinical features | Total no of cases | Parasite positive | Parasite negative |
|--------------------------|-------------------|-------------------|-------------------|
| Enlarged palpable spleen | 64 | 27 | 37 |
| Abdominal pain | 7 | 2 | 5 |
| Palpable liver | 6 | 1 | 5 |
| Lung signs | 17 | 9 | 8 |
| Frequency of stools | 4 | 3 | 1 |
| Herpes labialis | 2 | 2 | |
| Unconscious state | 4 | 2 | 2 |

Pulmonary manifestations of malaria are well known and they may vary from bronchitis to consolidation, lobar or lobular in type. Lung signs in 9 positive cases of malaria consisted of

3 cases Lobar consolidation (both peripheral and sternal positive) All *pl falciparum*

4 cases bronchitis (3 cases both positive one case sternal alone) *Pl. falciparum* crescents

2 cases pain in chest and dry cough

Peripheral smears and sternal smears were taken because of the presence of palpable spleen

Three positive cases of diarrhoea complained of fever with rigor and they had palpable spleen. Two of these cases had dysenteric symptoms viz frequency of stools with blood and mucous. Stool examination revealed a picture resembling that of bacillary dysentery. All of them responded to quinine. All these cases showed the presence of parasites both in peripheral and sternal smears.

There were 2 cases of cerebral malaria in the present series. Both of them, were admitted in an unconscious condition, one with a history of having fever with rigors for 8 days whereas no history was available in the second case. Both of them had palpable spleens. 1st case was stuporous and was not responding to any questions. Diagnosis was quite easy because of history of fever with rigor and palpable spleen. Both peripheral and sternal smears showed infection by *Plasmodium falciparum*. He was treated with quinine injections and he made an uneventful recovery. The second case was unconscious passing liquid stools every few hours. There was no blood or mucous in stool. Lower limbs were very rigid with marked exaggeration of deep reflexes and presence of ankle and patellar clonus. Plantar reflexes were extensor on both the sides. There was no rigidity of neck. Temperature on admission was 98.8°F. Diagnostic lumbar puncture did not reveal any abnormality. Both peripheral and sternal smears revealed a very heavy infection with *Plasmodium falciparum*. Practically every red cell was packed with one or more rings of malignant tertian parasite. He was treated with both oral and parenteral quinine in adequate doses. Temperature rose upto 101°F and then came down to normal on the second day and remained so for about twenty hours. His general condition did not improve at all and on the fourth day patient died with a temperature of 100°F. Peripheral smear showed the same heavy infection of *Plasmodium falciparum* on all days in spite of large doses of quinine. Post-mortem examination confirmed the diagnosis.

Fever with rigor in our country is commonly due to malaria but it is not always so. Some of these cases of fever with rigor admitted as malaria turned out to be 2 of meningococcal meningitis and one each of typhus, typhoid, pneumonia and septicæmia due to sub acute bacterial endocarditis.

These two cases of meningococcal meningitis were admitted in an unconscious condition with a history of fever with rigor. There was no rigidity of neck or lower limbs and both had enlarged spleen about two to three fingers below the costal margin. Clinical diagnosis of cerebral malaria was made in both these cases. Both sternal and peripheral smears were negative and cerebro-spinal fluid examination revealed typical findings.

Two cases were admitted with the history of fever with rigor going upto 102° to 103°F every day and coming down to normal with perspiration in about four to six hours. Spleen was palpable in both the cases. There were no abdominal symptoms nor any toxæmia. Sternal and peripheral smears were negative. Clinically they looked very much like malaria and so therapeutic test was tried but they did not respond.

to quinine and the same type of temperature continued. Serological tests were done—one was strongly positive for typhoid and other for typhus.

One case was referred by a general practitioner as a case of resistant malaria not responding to quinine. Just like a case of malaria, he was getting fever with rigor coming down to normal with perspiration, of six weeks duration—Spleen was palpable two fingers below the costal margin. He had moderate degree of anaemia with a systolic bruit heard all over the pericardium but heard best at the pulmonary area. Quinine by mouth or injection had no effect. Sternal and peripheral smears were negative. Blood was sent for cultural examination and Widal's test thinking it to be an enteric case just like the one mentioned above. The report of the cultural examination was "Streptococcus Viridans grown". Obviously this was a case of septicaemia due to sub-acute bacterial endocarditis.

Leucocyte count Total white blood cell count was done on 40 cases out of 70 indoor cases. In most of them the characteristic count was leucopenia with relative lymphocytosis and an increase in the large mononuclear cells. In 4 cases, leucocytosis was found varying from 10,000 to 21,400/c m m of blood. The highest count found was 21,400/c m m of blood with 56% polymorpho-nuclear leucocytes, 36% lymphocytes, and 8% large mononuclear cells. This was a case of benign tertian malaria.

Complications of sternal puncture

It is a very simple procedure and almost a painless one. With proper care, as described above, there should be no complication at all. Unfortunately in the present series we had some complications in two cases—one case developed small subperiosteal abscess and the other superficial osteomyelitis for which the latter case was to be hospitalised for a couple of days. Small subperiosteal abscess was treated from the out-patient department.

These complications occurred in our first fifty cases and were definitely due to lack of proper aseptic precautions, as in some of these cases sternal punctures were done on outpatient department cases without removing the hair from the sternum. Subsequently with proper aseptic precautions, there was no complication in the remaining 125 cases.

Response to treatment

Though we have got specific drugs for malaria, some cases particularly of cerebral type with a very heavy infection with plasmodium falciparum do not respond to treatment. Internal capillaries in such cases, are completely blocked by red blood cells containing sporulating parasites, which make the red blood cells, very sticky. Sometimes subsidiary measures like lumbar puncture, saline infusions, glucose and stimulants along with quinine may be useful. In the present series, one case of cerebral malaria due to plasmodium falciparum died in spite of early and intensive treatment with quinine. Other subsidiary measures like lumbar puncture, salines, stimulants, etc. were also used. Peripheral smear examined on the day of his death and that was the fourth day of disease, revealed the same heavy infection with malignant tertian parasites as was seen on the day of his admission to the hospital.

which was the first day of his disease. In spite of intensive treatment with quinine (of about 50 grs per day—30 grs of intra-muscular injection and 20 grs by stomach tube) for 4 days, the same heavy infection persisted. It was suggested that the ampoule administered may not be containing quinine at all. So one ampoule from the same box was sent for analysis and it revealed that the ampoule did contain adequate amount of quinine as claimed on the box. This was a case of cerebral malaria described above who had a very heavy infection with *Plasmodium falciparum*.

Though there are some cases, which do not respond to quinine as described above, we do come across some cases of malaria that get cured, at least so temporarily without any drugs whatsoever. This is probably due to immunological response of the patient to the infection and development of active immunity against malaria. In the present series, there were six cases of malaria, five of benign tertian and one of malignant tertian, who became normal after four to six rigors without any treatment. These cases were followed for one month during which time they did not get any relapse.

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(I am very thankful to the Dean, K E M Hospital Dr N K Sahar and Dr Mangaldas J Shah for allowing me to utilise this clinical material. Dr M J Shah encouraged me to undertake this study for which I am very grateful to him.)

DISCUSSION

Dr L Monteiro enquired whether the speaker had come across any exo-erythrocytic forms of the malarial parasites during the examination of the Sternal Marrow smears. He also wanted to know whether the immature cells of the erythroblastic series were parasitized.

Dr J K. Mehta in reply said that he had not observed the exo-erythrocytic forms. In reply to the other question, the speaker said that he had seen the parasites within normoblasts.

DEMONSTRATIONS OF HYPNOTIC PHENOMENA

by

K A J LALKAKA

K. E. M. Hospital, BOMBAY

About three years ago I had the privilege of demonstrating 2 cases of hypnotic phenomena before this Society. Since then I have come across some interesting experiences which I would like to relate shortly before I proceed with the demonstration of to-day's case.

1 A depressed looking young man came to me with the history that some times he becomes speechless and experiences great difficulty in expressing his thoughts. He could not consciously account for it.

Under hypnosis there was a marked abreaction. He burst into tears and in a fearful voice described his frustration in love and his secret determination to end life. He had spoken to nobody about his latent suicidal intent and was caught in time for psychotherapy which enabled him to face the reality more manfully.

2 On a very co-operative and accessible subject, I tried out the famous Rope Trick. He was put in a somnambulistic state. To all intent and purposes he looked wide awake, but in reality he was in a deep trance.

The verbal picture of the complete rope trick was presented to him. He appreciated every detail of it, as his replies to my questions showed. He considered himself very lucky to have witnessed it with his own eyes.

Then he was requested to write the full description of what he had witnessed and to sign and put the date. He wrote a vivid and accurate description of what he had seen. Later when he was brought out of the hypnosis he had no recollection of what he had seen or written and yet the signed document might stand as a proof to many for the genuineness of the rope trick.

3 A young man had gone extremely sensitive to noise. He could not concentrate on his studies if there was the least bit of noise and failure looked large in front of him.

Under hypnotic treatment he got over this sensitivity to noise and was able to concentrate. He of course passed.

4 A middle aged man had to leave his job temporarily and undergo treatment for his alcoholism. Being nervous and ashamed he would not give out the amount he imbibed during his last drinking bout but would only admit that he took about 4 peps a day.

Under hypnosis he revealed that he had steadily consumed about a bottle a day. Just after he came out of hypnosis he was asked again about the quantity. He repeated the old story of 4 peps. Then a terrified look came on him and he asked in anguish 'Did you ask me the same question while I was under and did I blurt out the exact amount?' Here was one of the rare occasions when I had to tell a lie in the beginning, in order to pacify him.

A paper read before 78rd meeting of Sheth G. S. Medical College and K. E. M. Hospital Staff Society on 9-8-47 with Dr. N. D. Patel in the chair.

This man had made up his mind to withhold the fact and yet under hypnosis it came out against his will

Here analysis done under hypnosis stole a march over psychoanalysis done during the conscious state. Through this method of free association we can overcome the unconscious resistance but not the conscious

I need not emphasize the fact that before a case is taken up for treatment by hypnosis, he should be overhauled physically for factors which may be partly or wholly responsible for his symptoms and also psychological analysis done in the conscious state

Some of the important therapeutic uses of hypnotism may be mentioned

- 1 Hypno analysis for
 - a war neurosis (shell shock)
 - b other forms of neurosis (conversion hysteria)

Here recovery of the painful forgotten memories and relieving of the repressed emotions (abreaction) occurs

- c cases of amnesia
- 2 Somnambulism or sleep walking
- 3 Fugue and dual personality
- 4 Spasmodic status like asthma and others
- 5 Neuralgia, headache
- 6 Insomnia
- 7 Stammering
- 8 Psychotherapy, producing mental relaxation and integration
- 9 Surgical use—induction of anaesthesia
- 10 Cure of habits like alcoholism

Before the subject comes in, let me give you a few of the salient points that I would like to bring out in the demonstration

1 Production of functional paralysis and other muscular phenomena

Here the psychological mechanism is similar to what happens in conversion hysteria with this difference that, for instance, the functional paralysis seen in hysteria is due to an unconscious wish on the part of the patient to develop that disability while here in hypnosis it is due to the state of hyper-suggestibility brought about by the willing co-operation of the subject

During the first world war, about 30 years ago, I saw the case of an Indian soldier who was evacuated from the battlefield to the Karachi War Hospital because his right hand would continue to move in a revolving way in front of his chest. The arm had frequently to be bandaged to prevent this motion. No organic lesion was detected. It was no doubt a case of conversion hysteria, brought about by an unconscious wish to escape the horrors of warfare

2 Induction of anaesthesia—the skin becoming insensitive to pains

3 Revival of forgotten memories

I wanted to test whether something which he could not recollect in his conscious state be brought out under hypnosis. So in the conscious state prior to putting him under hypnosis I asked him to repeat the names of his school teachers when he was in the 6th standard. He gave me six names but could not collect the names of the remaining two. He was urged to try harder but still could not succeed. He was then hypnotised and under hypnosis it was suggested that the two

missing names will come to his mind. He was then given a piece of paper and a pencil. Among the names he slowly scrambled out the two forgotten ones.

After he came out of the trance, the paper was put before him and he recollected the act of writing. He said that he was aware he was writing, but did not know what he was writing. He was glad to discover the two missing names.

4. Creation of a vision by initial suggestions.

5. Post-hypnotic suggestions where the subject after waking up from the trance carries out instructions or suggestions given under hypnosis without knowing the reason why.

Critical Notes and Abstracts

ACUTE CORONARY INSUFFICIENCY AN ENTITY

Shock, Hemorrhage and Pulmonary Embolism as Factors in its Production. During the past decade, considerable progress has been made in the study of acute coronary artery disease and myocardial infarction but not until recently has it been generally recognized that myocardial necrosis or infarction may occur in the absence of acute coronary occlusion. This type of acute myocardial disease we have termed "acute coronary insufficiency" (myocardial infarction without acute coronary occlusion).

Acute coronary insufficiency is a deficiency of the coronary circulation due to discrepancy in the demands of the myocardium and its available oxygen or blood supply. The term should not be construed to include acute thrombotic occlusion of the coronary artery. It is used solely to indicate *dysfunctional insufficiency of coronary flow which is usually transient and reversible although its effect on the myocardium may be permanent.* Acute coronary insufficiency possesses not only a distinct pathologic physiology, definite predisposing factors and a characteristic electrocardiographic pattern but also demands definitive therapeutic measures and it is thus a complete clinical entity.

Acute coronary insufficiency is provoked by factors which increase the work of the heart and decrease coronary blood flow. *When the myocardial ischemia is severe or protracted, myocardial necrosis or infarction may develop without acute coronary occlusion.* The factors precipitating acute coronary insufficiency fall into three groups: (1) Sudden increase in cardiac work through increase in blood pressure, heart rate or cardiac output. This condition may occur following severe physical exertion, emotional stress, tachycardia, hypertensive crises, acute thyroid crises, acute infectious states or drugs, such as adrenalin or pituitrin. (2) Diminution of coronary blood flow by means of suddenly lowered blood pressure and diminished cardiac output. This condition is observed following shock and peripheral collapse due to any cause, hemorrhage, acute hypotensive states, extreme bradycardia, heart failure, diminished circulating blood volume and acute abdominal catastrophes. (3) Interference with oxygenation of the blood with resultant impairment of its oxygen carrying power. Myocardial anoxia

may result from generalized anoxia, *e g*, asphyxia, recurrent pulmonary embolism, acute pulmonary diseases and bronchial asthma. A combination of the three types of causative factors inducing acute coronary insufficiency frequently occurs.

PATHOLOGIC ASPECTS The degree and extent of the myocardial changes that take place in acute coronary insufficiency vary with the duration and severity of the precipitating and predisposing factors. The gross picture is characteristic and usually consists of small, focal disseminated areas of tawny, mottled or hemorrhagic subendocardial discoloration in the left ventricle. The changes may occur in any portion of the ventricle, but they are generally most evident in the papillary muscles, especially the posterior, and in the left posterior wall and the left ventricular aspect of the septum. Focal infarction of the right ventricle occurs but it is relatively uncommon. Pericarditis has never been observed. Mural thrombi have been seen rarely. Careful and detailed search has failed to reveal recent occlusion of a coronary artery although there may be arteriosclerosis with mild to severe narrowing of the lumen.

THE ELECTROCARDIOGRAM The differences in character and location of the infarctions in acute coronary insufficiency and in acute coronary occlusion are reflected in the distinctive electrocardiographic patterns of the two conditions. The electrocardiogram of acute coronary insufficiency discloses depression of the S-T interval and flattening or inversion of the T wave in two or more leads. Except in rare instances, elevation of the S-T segment and deep Q waves, so characteristic of acute coronary occlusion do not occur in acute coronary insufficiency. The maximal changes may regress in serial records if the coronary insufficiency is ameliorated. Duration of the changes depends on the severity of the myocardial ischemia; they are often transitory if the factor precipitating the ischemia is rapidly abolished. Electrocardiographic alterations of relatively short duration usually indicate reversible anoxic or ischemic changes, and not anatomical myocardial lesions.

CLINICAL ASPECTS The simplest and most common clinical expression of acute coronary insufficiency is angina pectoris. This is a transient episode of coronary insufficiency, initiated by effort, emotion, or other factor which increases the work of the heart in the presence of pre-existing coronary arteriosclerosis. This condition is manifested clinically by substernal pain which is commonly transitory and relieved by rest or vasodilators. In the more severe type of acute coronary insufficiency the clinical picture may simulate that of acute coronary occlusion. Chest pain occurring during rest as well as after effort, shock, impaired heart sounds, drop in blood pressure, fever, leukocytosis, and rapid sedimentation rate may be noted. The severity of the clinical symptoms depends on the degree of myocardial ischemia and the extent of the infarction. As a rule, the clinical signs are not as marked as they are in acute coronary occlusion, and on occasion, they may be entirely absent. For adequate prevention and management of acute coronary insufficiency, it is essential that the precipitating agents be recognized by surgeons as well as by internists. The most important of the precipitating factors are *shock, hemorrhage, and pulmonary embolism*.

PREVENTION AND TREATMENT A question may arise of the clinical value of differentiating myocardial infarction due to coronary occlusion from myocardial infarction due to acute coronary insufficiency, since the systemic effects of both types of infarction differ only in degree. In answer, it may be pointed out that the therapeutic approach to each differs in several important respects and the etiological mechanisms involved are entirely dissimilar.

In acute coronary insufficiency active and vigorous measures in the early stages, directed toward removal or amelioration of the precipitating factor, may be successful in diminishing the myocardial ischemia or anoxia, and thereby preventing myocardial infarction. When infarction has occurred, elimination of the coronary insufficiency by appropriate therapy will prevent further cardiac damage. In acute coronary occlusion on the other hand, therapy is necessarily symptomatic, it is not based on specific measures or directed toward a special precipitating factor. It is worthy of emphasis that *measures ordinarily contraindicated in acute coronary occlusion may be of benefit in acute coronary insufficiency*. Treatment of acute coronary insufficiency depends almost entirely on the nature of the precipitating factor. Paroxysmal tachycardia may be terminated by vagopressor drugs, quinidine, or digitalis. In hypertensive crises, measures to decrease pressure such as vasodilators and phlebotomy are urgently indicated. In thyrotoxicosis, adequate medical treatment, and often thyroidectomy, are required to restore normal coronary circulation. In acute coronary insufficiency due to diminished coronary blood flow the treatment revolves about the proper management of shock and hemorrhage. Restoration of circulatory blood volume, arterial blood pressure and hemoglobin level by measures such as intravenous administration of blood is requisite. Although these measures may appear heroic and even harmful in a clinical condition which simulates acute coronary occlusion, nevertheless active treatment of shock and hemorrhage should be undertaken, particularly in patients of the older age groups whose coronary artery circulation is chronically deficient.

(A. M. Master, M.D., S. Daack, M.D., A. Grishman, M.D., L. E. Field, M.D., and H. Horn, M.D.
Condensed from the *Journal of the Mount Sinai Hospital*.)

METHIONINE AND VITAMIN SUPPLEMENTS IN HEPATIC DISEASE David Cayer has reviewed the efficacy of methionine and vitamin supplements in the treatment of 18 patients with hepatic disease. It was stated that the concepts of origin and therapy of hepatic disease have changed rapidly in recent years. The belief that cirrhosis is caused by toxic substances, most notably alcohol, is being replaced by the concept that the primary etiologic factor is probably a dietary deficiency or that multiple etiologic agents, acting through a mechanism which produces fatty infiltration of the liver, may be responsible. This concept is supported by the experimental production of cirrhosis in animals deprived of proteins, amino acids and vitamins.

On this basis the action of methionine was stated by early experiments to have shown that ingested protein is lipotropic and that the amount of fat found in livers of animals fed a deficient diet was inversely proportional to the amount of protein and carbohydrate in the diet. The lipotropic action of methionine was thought to be dependent on its

ability to provide methyl groups for the formation of choline. In the 18 patients studied all the patients received a daily oral supplement of methionine. These patients were divided into three groups. Group (1) consisted of four cases with acute infectious hepatitis, group (2) consisted of six patients with chronic hepatitis, and group (3) consisted of eight patients with chronic hepatitis and ascites (advanced portal cirrhosis of the liver). Vitamin supplements of 10 to 15 mg. nicotinamide, vitamin A, vitamin C, and vitamin K were given to those patients in whom it seemed to be indicated.

The authors concluded that the use of vitamin supplements and high calorie diets containing increased amounts of protein and carbohydrates is important in mobilizing the lipids of the liver, repairing hepatic damage and restoring hepatic function. Experimental as well as clinical observations indicate that the administration of excessively large amounts of nicotinamide may further decrease the methylating ability of the damaged liver and is unwise in view of the diminished ability of the liver to utilize and break down this vitamin.

The efficacy of methionine in the prevention and treatment of experimental hepatic injury appears to justify its clinical use. When given orally in daily doses of 8 gm. to the patients in this series, it appeared to be most beneficial in cases of chronic hepatitis without ascites. No beneficial effect was noted in patients with acute infectious hepatitis.

(Cayer, David, Bowman Gray School of Medicine, Winston-Salem, North Carolina. *Archives of Internal Medicine* 80: 644-654, November, 1947.)

DOLOPHINE Ishmael and Stacy have reviewed the literature on the use of Dolophine (Dimethylamino heptanone-Methadon) in the control of pain in bone and joint disorders. The authors reviewed investigations and results of previous observers, gave a brief outline of the pharmacological and clinical nature of the drug and listed the disorders causing pain in 106 patients. Classification was made as to the efficacy of the drug in controlling various types of pain which indicated that there was no great specificity in the use of the drug, except in the control of disogenic nerve root pain.

The authors concluded that Dolophine, also known as Amidon or Methadon, is a satisfactory analgesic for use in control of bone and nerve root pain. Its chief use is in patients whose pain is too severe for aspirin and too chronic in nature for morphine. They stated, however, that in using this drug, the possible danger of habituation should be borne in mind until further extensive clinical use definitely establishes the drug as habit forming or otherwise.

(Ishmael, William K., The University of Oklahoma School of Medicine and McBride Clinic, Oklahoma City, Oklahoma, and Stacy, John R. *Journal of the Oklahoma State Medical Association* 40: 464, November, 1947.)

ANTICOAGULANTS IN TREATMENT OF HEART DISEASES On the basis that thromboembolic phenomena caused terminal fatal episode in the lives of more persons over 50 than any other mechanism, Wright and Foley have reviewed the use of anticoagulants in the treatment of heart diseases with special reference to coronary thrombosis, rheumatic heart disease and subacute bacterial endocarditis. They concluded that a large proportion of the patients observed survived their first episode of thrombosis but later died of recurrence or complications.

Believing that treatment of heart disease in the past, while helpful,

has in many ways tended to encourage further thrombosis, the very complication most important to avert, the use of anticoagulants heparin and dicumarol constitutes a logical procedure to combat this tendency to thrombosis. Results of anticoagulant therapy in the treatment of thrombophlebitis of the peripheral veins was studied and it was stated that they appear to demonstrate conclusively that this form of therapy is the most satisfactory used to date. The evidence in favor of the value of anticoagulant therapy in the treatment of coronary thrombosis with myocardial infarction, especially in the presence of thromboembolic complications, was definitely encouraging.

The authors believe that final evaluation of results of this treatment must await carefully controlled studies on large number of patients—a study such as is now being carried on in 15 participating hospitals under the auspices of the American Heart Association and the United States Public Health Service. Evidence for the specific value of the addition of anticoagulant therapy to penicillin in the treatment of subacute bacterial endocarditis was found to be inconclusive at present, but it is believed that the increased tendency to thrombosis produced by massive doses of penicillin should receive further study in relation to benefit of combined anticoagulant therapy.

Even though results of anticoagulant therapy reviewed are still preliminary, the authors believe that results have so far been encouraging beyond expectation and that they justified more extensive exploration.

(Wright, Irving S. Department of Medicine, Cornell University Medical College, New York
New York and Foley, William T. The American Journal of Medicine 3 718 789 December, 1947.)

PROPYLTHIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM McCullagh, Hibbs and Schneider summarize the therapeutic properties of thiouracil and discuss some of their experiences in treating 218 cases of hyperthyroidism with propylthiouracil. Their studies convinced them that the latter drug is decidedly superior to thiouracil in the treatment of hyperthyroidism. They believe that propylthiouracil is as effective as thiouracil in about half the dose and is much less toxic in side effects. These findings were in accordance with previous reports. The authors arrived at the following conclusions:

- 1 Propylthiouracil is a safe drug. In 218 cases treated for an average of 8 months and in some as long as 14 months, no cases of agranulocytosis occurred. Three minor reactions occurred and four others required cessation of treatment.

- 2 It is effective in controlling hyperthyroidism of all types except possible instances of acute crisis in which its action is too slow. The hyperthyroidism of acromegaly may also be an exception.

- 3 An effective dose in more than 95 percent of patients was 300 mg per day. A smaller dose is effective in many cases.

- 4 Iodine in doses as high as 30 mg per day may be used concurrently with propylthiouracil. This eliminates thrill and bruit in diffuse glands and does not hinder the action of propylthiouracil.

- 5 The probable frequency of permanent remissions of hyperthyroidism following the use of propylthiouracil cannot yet be properly estimated. At present long-continued use of the drug appears warranted in some patients and may later appear feasible and perhaps desirable in many.

(McCullagh, E. Perry, Department of Endocrinology, Cleveland Clinic, Cleveland, Ohio, Hibbs, Ralph E. and Schneider, Robert W. The American Journal of the Medical Sciences 214 545 552 November, 1947.)

THE CHEMOTHERAPY OF LEPROSY Herman Gray reviews the attempts made to find a drug or drugs useful in the cure of leprosy. Etiology, symptomatology, pathology and diagnosis and prophylaxis of the disease were discussed. There was discussion of the evaluation of drugs and treatment, such as chaulmoogra oil (Heiser-Mercado mixture), gynocardic acid and gynocardates, arsenical compounds, antimony and copper salts, gold salts with carbon dioxide snow, nastin (ether-extracted portion of acid-fast bacilli from human leprosy tubercles), bacterial vaccines, protein shock therapy, vitamins, sulfone drugs, particularly Promin, and finally, antibiotics.

The sulfone drugs were first used in leprosy in 1941. Promin has been given to almost 200 patients at the Carville Leprosarium since that date, and the majority of these people had moderately to far advanced lepromatous leprosy. The results over these five years have been very encouraging, for almost all patients showed some improvement and about 40 percent in one reported series had a reversal of the skin smear formerly positive for lepra bacilli. Advanced nodular lesions slowly resolved, and the patients noted a generalized improvement in themselves. The drug was described as at least "the most beneficial of any drugs yet tried." Whether its action is chemotherapeutic is not known. Toxic effects consist primarily of the production of anemia and more rarely skin rash. Diazone and promizole, two other sulfone drugs, have been given by mouth, and their effect on the disease have been of about equal intensity to that of promin. The toxic effect was principally hemolytic anemia, occasionally skin eruptions and nausea and vomiting.

Several reports on promin and diazone from Latin America and Africa have been as favorable as those from Carville.

Streptomycin has been begun on a small group of patients at Carville, but no reports are as yet available. The authors conclude that while caution is necessary in ascribing antileprotic qualities to any drug, these recent developments of sulfones and antibiotics have brought to the fore possibilities that a true chemotherapeutic agent may soon be discovered.

(Gray, Herman. Los Angeles Co. Gen. Hosp., Los Angeles, Calif., New Orleans Medical and Surgical Journal 100: 218-230 November, 1947.)

PERSONALITY DISORDERS IN GASTROENTEROLOGY

Sullivan and McKell report on personality disorders occurring in the gastroenterology section of the Ochsner Clinic of New Orleans. Five hundred cases were analyzed. Among these were 62 cases of peptic ulcer, 35 cases of cholelithiasis, eight cases of epigastric or diaphragmatic hernia, 11 cases of carcinoma and seven cases of cirrhosis of the liver. In each of the 500 cases presented, a study of personality disorders was made with the hope of presenting an integrated picture of the people who came to the gastroenterology clinic rather than of the digestive tracts.

The cases were divided into three groups: (1) purely functional diseases, (2) the "psychosomatic affections" and (3) organic lesions. In group (1) the symptoms complained of were often vague or symbolic, such as weakness or deep ache, bad taste in the mouth, pressure or nausea. In group (2) symptoms were more definite and usually well localized and in group (3) they were generally so well localized the

patient could point to the cause of his distress with one finger. Group (1) showed day to day variability of symptoms, group (2) periodic occurrence and group (3) little change. Patients in group (1) always had related mental disorders. In group (2) emotional disturbances were often but not always related to the illness and usually preceded the symptoms. In group (3) it was found that emotional disturbances might follow symptoms or be completely unrelated to them. Examples of group one were given as nervous indigestion, cyclic vomiting, nervous diarrhoea, and spastic colon. Examples of group (2) were peptic ulcer, mucous colitis, ulcerative colitis, and cardiospasm. Examples of group (3) were carcinoma, cirrhosis, cholelithiasis, and amebiasis.

Of all the cases studied, 42.2 percent fell into group one, with an average age at onset of 35.0, 29 percent into group (2), with an average age at onset of 36.9, and 28.8 percent into group (3), with an average age at onset of 43.5. There was a larger percent of males (270) than females (230) in the group. Among the 388 patients with definite personality disorders, 278 had anxiety state, 64 depressed state, 22 fatigue state and 19 showed conversion hysteria.

The authors stated that an important concept which to them had been of great value in therapeutics was that, when it could be shown that personality traits, environmental stresses and moral influences had resulted in decompensation expressed by gastrointestinal symptoms, much more could be accomplished in therapy directed toward compensation the patients in all of these spheres, and that any physician who directs his efforts exclusively to the correction of organic gastrointestinal diseases will find himself highly successful only in the cases of patients which fall into group (3), or 28.8 percent of patients.

(Sullivan, Albert J., Ochsner Clinic section on Gastroenterology, New Orleans, La., and McKell Thomas E.: *Gastroenterology* 9: 524-538 November 1947)

THE ACTION OF PTEROYLGLUTAMIC CONJUGATES ON MAN In "Science," December 19, 1947, Sidney Farber et al., (1) report on the action of pteroylglutamic conjugates on man, following animal experimental studies by Leuchtenberger et al., (2) in which it was shown that L casei inhibited the growth of transplanted sarcoma in 180 female Rockland mice. In 1945 Lewisohn (3) continued these studies and demonstrated occurrence of complete regression of about one-third of the single spontaneous breast cancers observed in three different strains of mice treated with daily intravenous injections of five micrograms of fermentation L casei factor. At the time of these experiments the substance used was thought to have been folic acid. However, it has since been demonstrated that the substance used was a conjugate of folic acid (pteroyltriglutamic acid).

In these experiments 149 mice of three different strains from the Jackson Memorial Laboratory, strain A, Rockland strain and Bagg strain, all of which bore single spontaneous breast cancers diagnosed by biopsy were used. One hundred twenty of the mice were divided into two groups of 60. One group received daily intravenous injections of five micrograms L casei factor over a period of four to six weeks. The control group was untreated. Intravenous injections of five micrograms of L casei led to complete disappearance of the tumors in 38 of the mice. None of the tumors disappeared in the control group. Fourteen of the control group, however, developed new tumors, whereas only one new tumor was observed in the treated mice. The observation periods

extended from two to ten months for both treated groups and controls. During this time no local recurrence or new tumors were observed among 88 animals believed to have been completely cured by the treatment.

The material teropterin and diopterin used in studies by Farber et al were supplied by the Lederle Laboratories Division, American Cyanamid Company. These are synthetic compounds (pteroyltriglutamic acid, or teropterin and pteroyldiglutamic acid, or diopterin). These synthetic compounds were found to have microbiological activities identical with those of the naturally occurring fermentation L casei factor, although diopterin is only slightly active. Farber et al, working in the Children's Hospital, the Peter Bent Brigham Hospital, and New England Deaconess Hospital and Departments of Pathology and Surgery at Harvard Medical School, Boston, treated 90 patients having malignant disease with these substances.

The patients selected were those for whom established therapeutic procedures apparently offered no hope of cure. All of these patients had advanced neoplastic disease and most of them had metastases. The series included patients with acute leukemia, astrocytoma, Ewing's tumor, carcinoma of the rectum, colon, stomach, cervix, prostate, pancreas, esophagus, bladder, breast, gall bladder, kidney, and ovary, and Hodgkin's disease. Patients with lymphosarcoma, osteogenic sarcoma and other rarer types of tumors were also included. The patients varied in age from under three years to over 71 and the duration of treatment varied from a few days to five months, average length of treatment being about five weeks.

Daily dosage varied from 10 to 150 milligrams of teropterin intramuscularly, although some patients received as much as 500 milligrams intravenously. Dosage of diopterin averaged from 20 to 300 milligrams per day daily.

The authors believe that initial treatment calls for 20 milligrams daily of either substance for one week, after which the dosage may be raised to 50 milligrams per day for two or three weeks longer. Both substances were dissolved easily in from one to eight cubic centimeters saline for intramuscular or intravenous administration. There were no reactions following intravenous administrations and no important local reactions following intramuscular administrations other than that some of the patients complained of local burning or aching sensations lasting several hours. The reaction was said to be usually no worse than that following intramuscular injection of penicillin.

No systemic reactions occurred. Important changes in pulse, respiration, or temperature or significant long-term variations in blood pressure were not observed. Post mortem examinations were performed on 18 patients with whom treatment had been carried out for a period of several weeks. Gross pathologic and histologic material available from these patients revealed no change in organs and tissues which could be regarded as a deleterious effect due to the medication employed. In no instance was evidence of pancytopenia, agranulocytosis, degeneration of the kidneys, liver or myocardium found. The authors state that in view of the limited number and short duration of their observations and the impossibility of ruling out the role of psychotherapy, they will postpone any definite conclusions concerning general effects of this treatment. However, adult patients expressed improved

energy, appetite, sense of well-being, and demonstrated less irritability and apprehension. In a few instances definite diminution of pain occurred, measured by reduction in amount of sedation or analgesin required.

Analysis of data collected showed that in certain instances conditions were such that a causal relationship was apparent between the administration of the glutamic acid compound employed and changes in the patient's condition or in the histologic appearance of the tumor obtained at biopsy or at autopsy. In a larger group of patients with a clinical picture complicated by use of more than one therapeutic agent, such as radiation therapy, observations suggested that the addition of the glutamic compound played an important part in patient improvement. Examples of these changes were temporary decrease in the size of multiple subcutaneous nodules of an aneplastic carcinoma, temporary decrease in size of metastasis to the lung from a carcinoma of the testis, degeneration and necrosis in pathologic specimens of tumors (two cases), and on two occasions, temporary reduction in the acid phosphatase level in the blood of a patient with multiple metastases to bone from a carcinoma of the prostate.

From preliminary studies, the authors conclude that use of terop-terin and diop-terin as employed in their studies are nontoxic and are in general suitable for clinical use. However, they cannot yet present evidence that these substances should be employed in the routine therapy of patients with cancer.

Case studies are continuing and final results of treatment on all 90 cases will be reported. The authors believe that it is too soon to attempt any accurate evaluation of action of these substances on neoplastic disease in man.

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(2 Leuchtenberger, C. Lewisholm, R.; Ianzlo, D.; and Leuchtenberger, R.; Proc. Soc. Exp. Biol. and Med. 55: 204, 1944.

(3 Leuchtenberger, R.; Leuchtenberger, C. Ianzlo, D.; and Lewisholm, R.; Science 101: 46, 1945.)

BLADDER MANAGEMENT FOLLOWING SPINAL INJURY Vesceen and his associates assert that genito-urinary complications are the chief causes of the high morbidity that follows spinal cord injury. Confusion and disagreement exist among urologists regarding the management of "cord bladder." The authors present a resume as to how such problems were handled with gratifying results.

The anatomy and physiology of the bladder-emptying mechanism are not completely understood. Theories rise and fall, but from these certain important factors have been established. The authors discuss the neural anatomy of the bladder and stress that the detrusor is the chief muscle involved in micturition. Impulses acting through parasympathetic fibers carried in the second, third and fourth sacral nerves and spinal centers in the conus medullaris provide the micturition reflex which is inhibited centrally.

The ultimate aim of the urologist is to assist nature in producing the return of normal bladder function or the closest alternative, the automatic bladder.

As can be seen from a review of the neural anatomy of the bladder, the level of the spinal injury may be used as a guide in prognosticating

the final result. Generally, those below first lumbar, involving the bladder nerves, hold the poorest urologic prognosis.

The first 48 hours following spinal injury is considered a crucial period by the urologist. When the case is seen immediately, the bladder is permitted to become distended. Catheterization is delayed as long as possible. The normal bladder musculature will not rupture spontaneously from such dilatation. Paradoxical incontinence will take care of this.

First, the patient is instructed to attempt to empty the bladder at periodic intervals by the clock. In the very beginning this interval may be as short as every 30 minutes. Gradually, it is increased until the interim between voidings is in the neighborhood of two to three hours. The accessory muscles of micturition, namely, the recti, obliques, and transverse of the abdomen and the diaphragm are utilized if possible. In addition, suprapubic pressure exerted with the closed fist is advised if the upper extremities are not involved in the injury. If such is the case, an attendant accomplishes the Crede maneuver. A residual urine will be present and will act as a culture medium for pathogenic organisms.

Antibiotic and chemical agents are administered from the moment the patient is seen. *Penicillin* is given in large doses, 40,000 units and up, every three hours. *Streptomycin* is reserved until complications develop because organisms are capable of developing considerable resistance to it. Infected cord bladders head the list of urological disorders for which this particular material is indicated. When administered, 0.4 gram is given intramuscularly every six hours. The sulfa drugs are administered in an acid medium and are effective. The dosage rarely exceeds 4 Gm. in 24 hours. *Methenamine*, *mandelic acid*, and *mandelamine* are also available.

Acidification of the urine is carried out with one of the following drugs: *Ammonium chloride*, *ammonium nitrate*, *ammonium mandelate*, and *sodium acid phosphate*. The acid-ash or ketogenic diet is utilized.

The acidification of the urine serves two functions. It produces an undesirable culture medium for the growth of *E. coli*, the most troublesome pathogen encountered, and assists in maintaining carbonates and phosphates in solution, staying off the development of urinary calculi, resulting from the mobilization of the skeletal salts during a protracted period of bed rest. Urine acidity is checked daily. The carbon dioxide combining power is checked periodically. The production of acidosis may be a serious problem in itself.

Acetyl beta-methylcholine may be used initially because of its parasympathimimetic action. Little may be expected from its use, but occasionally it will assist detrusor contractions. By its proper use the postoperative bladder atony may be completely controlled, obviating the need for catheterization. Oral doses up to 300 milligrams every 3 to six hours or parenteral doses up to 150 milligrams are employed. *Atropine sulfate* should be readily available to control and abolish its actions if the need arises.

During the first five days automaticity may develop. Such is not always the happy state of affairs. Catheterization may finally have to be done. The rapidity of decompression of the bladder is still controversial. No harm is done in completely emptying the bladder in acute

distention. Slow decompression is advised if the distention is of long standing. If, after the second catheterization, more are needed to promote drainage an indwelling urethral catheter should be placed. Proper catheter care is required (urine acidification, frequent irrigations with a buffered citrate solution) and frequent changes with the strictest of periodic drainage is used. At each catheter change the development of automaticity is checked. By gradually increasing the pressure as tonicity returns, automaticity may develop. Finally, after a lapse of several months or the development of complications (infection, sepsis, reflux, ureteral flow, hydro-and/or pyonephrosis) a temporary suprapubic cystotomy may be done. The suprapubic tube must be handled with the same care as an urethral catheter.

Transurethral resection of small amounts of tissue from the bladder neck of cord bladders has been popularized during the war years. Removal of the "hypertrophic" neck is supposed to promote urine drainage, do away with straining and residual urine, yet leaving the patient continent with good control. The patients under the care of the authors who have had transurethral resections in other hospitals were incontinent, necessitating a penis clamp. It is felt that the transurethral resection should be done late in the management of these cases.

(Veselen, L. L. Chicago, Ill., Miller W. W. Jr. and Paynter, G. C. United States Naval Med Bulletin, 47: 945-953 November-December, 1947)

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Original Contributions

ON TUBERCULOSIS

SOME OUTMODED CONCEPTS AND PRACTICES IN PHTHISIOLOGY

by

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I

The most inveterate concept of all among general practitioners is the long exploded fairy tale of the insidious apical onset of lung Tb. There are admittedly cases of apical Tb, but careful investigations have shown that they are mostly benign and only 7 per cent of them are apt to turn into a progressive disease. The initial lesion, be it the primo-infection in childhood or the re-infection of the juveniles and adults, is practically never found in the apices. The site of predelection of the primo-infection is mostly the base of the lung. During the post-primary stage (or secondary stage of Ranke) metastases may appear in the apices besides other parts of the lung (Simon foci, Aschoff-Puhl foci), where as a rule they remain quiescent. The onset of the tertiary stage, the clinical phthisis of juveniles and adults, is not insidious but it is an acute, pneumonic patch situated generally in the infraclavicular (subapical) region, generally termed as "Early Infiltration" (Assmann, Redecker). In extremely benign cases which, however, are rare this infiltration may quickly vanish without leaving any trace. In other favourable cases gradual regression with fibrosis can be observed. In the majority of cases, however, the infiltration undergoes a rapid cavernisation. Various clinical features described by the French school as lobite, cortico-pleurite, scissurite, etc., are but local modifications of the same acute phenomenon.

II

The obsolete concept of the apical onset is closely connected with the time-honoured idea that this onset of Tb can be detected by a physical examination. Much time is wasted by practitioners in painstaking percussion, auscultation and what not, of the apices. We have to admit by now that apical lesions are not to be detected by ever so elaborate physical examinations. Even the acute infiltrations of the sub-apical region will rarely produce any appreciable physical signs. ^{At the} ^{active} the examination does reveal such signs we can be sure that the process is already far beyond the initial stage. A physical examination always ^{negative} result is wholly unreliable and inconclusive in order to be done in the absence of Tb. The detection of an incipient Tb can be ^{versal} ^N

achieved only by X-ray examination. Every case rightly or wrongly suspected should be brought before the X-ray screen. By X-ray examination the initial lesion can be detected long before the classical signs and symptoms of the disease become evident, often even earlier than the detection of Tb-bacilli in the sputum. Burrell goes as far as to say "that no signs may be found even by an expert in a case of extensive disease, and that he may be faced with a legal action for negligence if he has based his negative diagnosis on the absence of physical signs and has not had an X-ray taken". The importance of X-ray examination for detecting Tb is at present widely recognised, and serial or mass examinations by screenings or miniature photos are recommended wherever the circumstances allow. Just as in many hospitals Wassermann tests are done with all patients as a matter of routine, X-ray examinations too should be taken up as part of the general examination for the simple reason that the incidence of Tb is by far greater than that of syphilis. The same applies to medical outdoor services. The X-ray examination of the chest has become part and parcel of the modern physician's duties. Mere percussion and auscultation will not reveal more to him than to a general practitioner. The view that X-ray examination is but an ancillary method is antiquated and should be eradicated.

Widespread ignorance prevails about the proper formulation of the diagnosis in Lung Tb. The layman knows that there are "degrees" or "stages" and is keen to obtain from the doctor as much specification as possible. If there are sufficient catarrhal and cavernous signs, the physical examination may be adequate enough to settle the diagnosis of a more or less advanced case. It is impossible, however, to specify any incipient or even moderately advanced form without the help of X-rays. Since the development of the so-called qualitative diagnosis by X-ray photos the mere statement of lung Tb as a clinical diagnosis has become utterly obsolete. For long it has been known that there are acute, subacute and chronic forms. The pathological anatomy has taught us that there are reparative and destructive processes, exudative, productive (proliferative) and fibroid processes, atelectases and emphysemata, etc. generally intermingled, with more or less visible predominance of one or the other. Many of these innumerable variations as well as their site and their extent can, to a certain degree, be depicted by the X-ray photo. Numerous proposals have been made to classify the kaleidoscopic manifestations thus revealed, and it is desirable that the physician should be acquainted at least with the most important of them which can be enumerated as follows —

- (1) Primary Lesion (Primo Infection, Primary Complex)
- (2) Tracheo-Bronchial Adenopathy
- (3) Juvenile Tb (comprising such forms as metastatic, infiltrative, pneumonic, hilar-lung Tb, epituberculosis)
- (4) Lympho-haematogenous Tb (Cohen)
 - (a) Acute Miliary Tb
 - (b) Chronic Miliary Tb (generalised or regional, Granulie froide (Burnand), Lymphadenitis reticularis (Schuermann), Miliaris discreta (Neumann), Tuberculosis fibrosa densa and diffusa (Neumann))
 - (c) Subacute or chronic, nodular (medium-sized) haematogenous Tb

- (d) Protracted, haematogenous, multiformous Tb
- (e) Transitional form of haematogenous Tb
- (f) Phthisis with extrapulmonary, haematogenous lesions
- (5) Early Infiltration (Assmann Focus)
- (6) Pneumonic Tb
 - (a) Caseous, lobar
 - (b) Broncho-pneumonic, lobular
- (7) Chronic fibro caseous Tb ("forme mixte")
- (8) Chronic fibroid Tb (sclerotic, enihotic)
- (9) Pleurisy (without parenchymatous lesions)

These clinical entities should be precisisonised by mentioning the site, the extent, the presence of cavities, the presence of positive sputum, the activity (whether progressive, stationary or regressive), the presence of effusion, pneumothorax or other sequelae of previous collapse therapy

III

Leaving diagnostics, let us have a look at some therapeutic aspects. Before the advent of the collapse therapy, at a time when organised Anti-Tb Campaign was still in its beginnings, a Tb-patient was straight away sent to a sanatorium, if he could afford it. Hospitals offered only very restricted facilities mostly reserved for acute cases and only for a short stay. When the collapse therapy came into stride, an unfortunate division in the therapeutic outlook took place, as many doctors were apt to differentiate between cases suitable for collapse-treatment at home or in a clinical institution near their residence, and those suitable for climatic treatment which generally meant conservative measures in a sanatorium. The attitude taken by the sanatoria at that time was not entirely blameless so that this deplorable division persisted for many years and even up to present times. All too long and too confidently the sanatoria relied upon their reputation and upon the hitherto undisputed and uncompeeted blessings of climatic factors, refusing to take up collapse therapy and to step into line with the general trend of modern therapeutics. A good example offers the famous sanatoria in Switzerland, many of which still at the beginning of the last decade considered their conservative outlook superior to all the "newfangled" interventions which were going on elsewhere. The last decade, however, saw a rapid recovery by the sanatoria of the lost ground, but among the public and many physicians there still lingers the idea that a "change of climate" is sufficient and an institutional treatment dispensable. To cut a long story short, we may say that at present there is no rivalry between an institutional treatment at home and that in a climatic station, provided that the proper therapeutic steps are taken at the proper time. In western countries, however, the opinion has recently gained much ground that a tuberculous patient is best treated in that climate where he is used to live and to work, because the sudden change of climate while returning from a hill station or from the sea shore may undo the obtained result and possibly cause a relapse. If we leave alone the fact that it is more probably the stress and strain of the sudden return to professional activity than the mere change of climate that may adversely affect the health of an ex-patient, we must be aware that this new western trend is not quite as suitable to our tropical India as it may be in a more temperate climate. Just as

everywhere else our biggest congregations of population are on a low level and for the greater part of the year exposed to excessive heat and moisture. Even at complete rest a patient in Bombay or Calcutta will hardly feel as comfortable as another one in London or New York. According to Mills "in the tropics it is mainly relief from the debilitating heat that is needed. With tuberculosis it is now recognised that stimulation of general nutrition is the most effective line of therapy, and that a stimulating climatic environment affords the best basis for improving nutrition. Particularly it is recognised that the disease runs a most rapid course in depressive heat and that patients in the tropics get marked relief by being transferred to altitudes above 5000 feet because of the more invigorating climate." Thus, for this country the immediate relief obtained by climatic factors appears to be more important than the possible dangers of a later return to a lower altitude.

Continuing the chapter of injudicious therapeutical practice, I should like to say a word about Gold-Therapy. When I came out here about 9 years ago I was surprised about the popularity of this treatment after I had almost forgotten its very existence due to the oblivion into which it has almost passed in western countries. Then I came to know that gold treatment in India has a traditional reputation dating from ancient times, a fact which may account for the popularity of the modern products as well. When a case has been diagnosed as Tb it has become an almost automatic reflex of our practitioners to prescribe gold injections, and it is against this indiscriminate and injudicious practice that I venture to put in an earnest word of warning. In the early days of gold treatment over 20 years ago our hopes were justified by the bactericidal effect of certain gold salts "in vitro". But, as it happens so often in medicine, the germs inside the human body behave differently from what was expected in the laboratory, and up to this day the mode of action of gold preparations has remained uncertain. There have been supporters of the view that gold salts have a stimulating effect on the natural defences of the body, others advocate the idea that their action is analogous to a catalyst affecting the reticular-endothelial system. These scientifically sounding conjectures are but poor subterfuges for our ignorance. On the other hand, negative statements, viz. that gold has no direct action on the Tubercle bacillus within the living organism, and that it has certain noxious potentials, have emerged as almost unanimous. We are, therefore, left with out any sound rationale at all for gold-therapy, and that is as bad as bad can be. Now, I quite agree with those who say that all scientific rationales may go to blazes if a success in practice justifies the use of a drug. But here again the literature of more than 20 years from all over the world shows such a degree of divergency of opinion that this alone is quite sufficient to put us on our guard. In fact, the most studious investigators have come to the conclusion that the alleged merits of gold depend on the normal proportion of improvements and recoveries which happen with any method, or without any method at all. In conclusion I venture to say that the money wasted and the risks involved in gold therapy are in no proportion to the more than questionable benefit it may have.

Turning to another aspect of therapy let us have a look at the collapse therapy. One may well ask what may be outmoded already there, the collapse therapy being our latest weapon in phthisiotherapy.

We should remember, however, that the A P treatment is almost half a century old, and that the initial technique of squeezing by hypertension-fillings did not take long time to become outmoded in favour of the hypotension or relaxing technique, which at present has been commonly accepted. There are, however, certain other hazardous details which some doctors from habit still adhere to. First and foremost I wish to caution against A P installations with an apparatus that does not allow the air to be sucked spontaneously into the pleural space, i.e. those contrivances where the escape of the air can be effected only by pressure, be it by a pump, a piston, or by the gravity of a gazometric bell. However convenient for ordinary refills such an apparatus may be, it should be shunned in cases of a primary A P. Many accidents can be avoided if during the first filling the manometrical readings are kept on the negative side. This question of the manometrical readings brings us to a second point of an outmoded technical detail, viz., those contrivances which do not allow the manometer to respond during the very act of filling. The possibility of checking the negative pressure while giving a primary filling should be an unconditional prerequisite of an up-to-date apparatus. Another dangerous practice is the introduction of the A P needle fitted to a syringe in order to ascertain by the free play of the plunger whether the needle has entered the pleural space. This manipulation together with the subsequent removal of the syringe to be replaced by the inflation tube is actually a provocation of accidents. The needle, the tube and the manometer should be a closed system without any cocks, valves and what not. In such a closed system the response of the manometer will inform the operator about the position of the needle with much greater sensitiveness than the plunger of the syringe, especially in a primary filling.

I may be allowed to make a short remark also on the Phrenic Nerve Operation. Ever since the inception of this operation there has been a vainglorious competition among surgeons on who can achieve his end by making the smallest possible incision. I am quite willing to congratulate myself for a nice and tiny button-hole incision in case of a phrenectomy with an evulsion of at least $4\frac{1}{2}$ to 5 inches of the nerve. If, however, an anticipated rupture of the nerve occurs, or in a case of a temporary interruption by crushing or alcoholisation, the necessity arises to search for accessory branches. Let us remember that in over 50 per cent of cases the nerve receives associate fibres above or below the usual site (Aycock et al). I have still to see the surgeon who is able to carry out a thorough search for associate branches while working through such a button-hole opening. With an incision of at least $1\frac{1}{2}$ inches, however, no difficulties can arise in this respect, many failures of the operation can be avoided, and the patient will be none the worse as regards the cosmetic result.

IV

If we turn our eyes to the vast chapter of bone and joint tuberculosis, we are aware of two trends in therapeutics. At the beginning of this century surgical intervention by resection was the only way of dealing with the focus wherever it was accessible. At that era the term "Surgical Tuberculosis" was coined as synonymous with bone and joint Tb. During the second decade of this century, however, this extreme was succeeded in turn by the other extreme of conservative rest com-

bined with heliotherapeutic or helio-climatic measures. At present we still find advocates of one extreme or the other, whereas the general trend is to arrive at a judicious selection of one or the other method, or better still a combination of both. Unfortunately there is a deplorable confusion as to the selection and timing of a surgical intervention be it with or without helio-climatic treatment. First of all, we have to understand that rest, immobilisation and relief from strain and pressure are the fundamentals in all forms of bone and joint Tb. Without these prerequisites climatic advantages or any amount of ultra-violet rays are of no avail at all. Any compliance of a doctor with patients or their relatives who refuse to submit to these fundamentals because of the inconveniences involved should be branded as bad practice. For the limbs, hips and shoulder joints, and for the cervical spine the plaster cast is still the method of choice for immobilisation and fixation. For the rest of the spine the plaster cast has many technical inconveniences, and the mere recumbent position is in most cases sufficient to arrest further progress of the disease, especially if the patient can be induced to maintain a perpetual prone position. The question whether in a given case a surgical intervention becomes necessary and when it should be done is such a complex matter that in this short survey only a few warnings against the most common mistakes can be given. The least evident but none-the-less deplorable malpractice is an injudicious delay of an operation, when after a reasonable time of expectance a conservative treatment does not show any satisfactory progress. This period may vary, according to the site and nature of the lesion, from 6 to 12 months, but rarely longer. It goes without saying that all too early operations, before the quiescent stage is reached, should be just as strongly condemned as any delay. Up to the age of 18 years no re-sections or amputations should be done. Above the age of 60 years the prospects of major operations are generally bad. The best result and a considerable shortening of the disease can be obtained by timely opening and excision of foci in the metaphyses or diaphyses of the long bones, in Tb of the calcaneum, and of extra-articular foci threatening to perforate into the adjacent joint. If in joint Tb after one year of observation the process is still progressing a resection or arthrodesis should be done. Any hope of saving a partial function of the joint is futile. The function of an apparently healed joint Tb with partially preserved function is like skating on thin ice. The best and safest result is a complete ankylosis which in cases ill-responding to conservative measures can be achieved by a resection in a much shorter time. Besides excision and arthrodesis, the third principle in surgery are those operations which by bone splints and grafts aim at a fixing and stiffening of the affected parts. I can only mention this last group of operations for the sake of completeness but I have to forego further details for the sake of brevity. In combination with helio-climatic measures a judicious indication for all these surgical possibilities should be the ideal to be aimed at by our specialty.

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NORMAL ELECTROCARDIOGRAPHIC STANDARDS FOR INDIAN SUBJECTS

by

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Normal Electrocardiographic standards have been worked out by numerous workers in Europe and America, the most notable contributions to literature being those of Lewis and Gilder (1912), Pardee (1933), McGinn and White (1933), Scham (1921), Shipley, R A and Hallaran (1936), Hoskin and Jonescu (1940)

Some of these standards, universally accepted as they are, are based on insufficient numbers of cases and apply to European or American subjects only. In view of the growing interest of the present-day clinician in the subject of Electrocardiography, a more thorough knowledge is required of the normal state of the electrocardiogram, with all its physiological variations and limits.

The following is a short resume of the work, undertaken by the author in 1939, and published in detail elsewhere (Vakil, 1940, 1941)

The figures, presented here, are based on a detailed study of 350 normal electrocardiographic records, (200 males and 150 females subjects)

Each subject was subjected to a thorough clinical investigation in order to rule out any form of cardiovascular disease or disorder. The tracings were taken with a Victor (G E C) portable electrocardiograph, with the subject at rest and in a sitting position, measurements were made in accordance with the standard technique.

The accompanying table, (page 116), gives the results of our investigations, in simple tabular form. The various deflections and "intervals" of the normal electrocardiogram are measured and analyzed, into age and sex groups, for the convenience of the over-busy practitioner of medicine.

SUMMARY

For the use of practitioners in India, a tabulated study is presented of the deflections and "intervals" of three hundred and fifty normal electrocardiograms. Variations due to age and sex have been noted.

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A Summary of the Main "Deflections" and "Intervals" of the Electrocardiogram

| Deflection | Feature Investigated | Sex | 1st DECADE | | | 2nd DECADE | | | 3rd DECADE | | | 4th DECADE | | | 5th DECADE | | | FOR ALL DECADES | | | Scale |
|--------------|----------------------|-----|----------------|--------------|--------------|----------------|--------------|--------------|----------------|--------------|--------------|----------------|--------------|--------------|----------------|--------------|--------------|-----------------|--------------|--------------|-------|
| | | | Aver | Min | Max | Aver | Min | Max | Aver | Min | Max | Aver | Min | Max | Aver | Min | Max | Aver | Min | Max | |
| P Wave | Amplitude | M F | 0.80 0.88 | -1.0 -0.3 | 3.1 3.1 | 0.00 0.80 | -1.1 -1.0 | 3.0 3.3 | 0.04 0.80 | 2.0 1.1 | 3.1 3.0 | 1.25 0.00 | -0.5 -0.2 | 3.1 2.1 | 1.05 1.05 | -1.2 -1.3 | 2.3 3.3 | 1.05 0.04 | -2.0 -1.3 | 3.1 3.3 | mm |
| | Duration | M F | 0.08 0.08 | 0.04 0.03 | 0.14 0.14 | 0.080 0.080 | 0.04 0.03 | 0.15 0.14 | 0.085 0.089 | 0.03 0.04 | 0.15 0.14 | 0.087 0.083 | 0.04 0.03 | 0.14 0.15 | 0.088 0.080 | 0.04 0.01 | 0.15 0.14 | 0.084 0.082 | 0.03 0.03 | 0.15 0.15 | sec. |
| QRS complex | Duration | M F | 0.060 0.057 | 0.04 0.04 | 0.10 0.11 | 0.068 0.067 | 0.03 0.03 | 0.11 0.11 | 0.070 0.068 | 0.05 0.04 | 0.11 0.10 | 0.070 0.077 | 0.04 0.00 | 0.11 0.10 | 0.070 0.075 | 0.04 0.05 | 0.11 0.10 | 0.072 0.073 | 0.03 0.03 | 0.11 0.11 | sec. |
| | Amplitude | M F | 0.37 0.57 | 0.0 0.0 | 0.0 1.3 | 0.57 0.50 | 0.0 0.0 | 0.0 3.8 | 0.50 0.54 | 0.0 2.7 | 3.0 2.7 | 0.42 0.48 | 0.0 0.0 | 4.2 3.0 | 0.31 0.39 | 0.0 0.0 | 3.4 5.0 | 0.48 0.50 | 0.0 0.0 | 6.0 5.0 | mm |
| R Wave | Amplitude | M F | 7.1 0.5 | 0.3 0.0 | 20.0 14.0 | 8.3 7.2 | 0.8 1.0 | 23.2 10.2 | 9.2 0.5 | 1.5 1.6 | 22.0 31.1 | 10.8 10.0 | 3.0 3.2 | 17.6 18.2 | 8.7 8.7 | 2.2 2.9 | 2.2 19.6 | 0.3 0.0 | 0.8 1.0 | 23.3 31.1 | mm |
| | Amplitude | M F | 1.42 0.77 | 0.0 0.0 | 10.0 0.7 | 1.55 1.11 | 0.0 0.0 | 10.1 7.1 | 2.15 2.22 | 0.0 0.3 | 0.3 0.3 | 3.06 2.50 | 0.0 0.0 | 7.8 8.3 | 2.00 3.05 | 0.0 0.0 | 5.0 7.2 | 1.00 1.07 | 0.0 0.0 | 10.1 0.3 | mm |
| T Wave | Amplitude | M F | 2.21 1.18 | -1.1 -1.0 | 9.3 6.3 | 2.31 3.10 | -4.2 -3.6 | 9.8 7.3 | 3.4 3.3 | -2.2 -3.1 | 8.1 10.1 | 1.7 1.5 | -3.3 -1.1 | 7.2 6.1 | 1.8 2.2 | -5.0 -2.0 | 7.1 10.1 | 2.1 3.1 | -4.2 -1.1 | 0.8 10.1 | mm |
| | Duration | M F | 0.101 0.170 | 0.08 0.08 | 0.25 0.26 | 0.173 0.177 | 0.10 0.10 | 0.20 0.28 | 0.160 0.160 | 0.12 0.13 | 0.20 0.22 | 0.150 0.107 | 0.10 0.13 | 0.24 0.24 | 0.107 0.171 | 0.10 0.14 | 0.26 0.24 | 0.169 0.171 | 0.10 0.10 | 0.26 0.29 | sec. |
| U Wave | Amplitude | M F | 0.53 0.30 | 0.1 0.3 | 1.5 1.1 | 0.50 0.43 | 0.10 0.20 | 1.4 1.2 | 0.55 0.75 | 0.30 0.20 | 1.4 1.4 | 0.50 0.60 | 0.10 0.10 | 1.2 0.80 | 0.60 0.50 | 0.10 0.20 | 1.2 1.1 | 0.54 0.37 | 0.1 0.2 | 1.5 1.4 | mm |
| | Duration | M F | 0.13 0.14 | 0.04 0.05 | 0.25 0.21 | 0.14 0.14 | 0.00 0.00 | 0.24 0.22 | 0.16 0.18 | 0.10 0.12 | 0.24 0.24 | 0.10 0.16 | 0.10 0.08 | 0.24 0.22 | 0.10 0.18 | 0.10 0.08 | 0.20 0.25 | 0.10 0.17 | 0.06 0.08 | 0.20 0.21 | sec. |
| P Q Interval | Duration | M F | 0.062 0.048 | 0.01 0.00 | 0.12 0.10 | 0.061 0.047 | 0.01 0.01 | 0.12 0.10 | 0.050 0.050 | 0.02 0.02 | 0.12 0.12 | 0.062 0.036 | 0.01 0.01 | 0.13 0.10 | 0.058 0.052 | 0.01 0.01 | 0.12 0.12 | 0.06 0.03 | 0.01 0.01 | 0.13 0.13 | sec. |
| | Duration | M F | 0.142 0.126 | 0.06 0.06 | 0.23 0.20 | 0.143 0.123 | 0.07 0.08 | 0.21 0.20 | 0.147 0.138 | 0.10 0.09 | 0.20 0.21 | 0.105 0.156 | 0.11 0.00 | 0.21 0.20 | 0.157 0.144 | 0.10 0.06 | 0.31 0.21 | 0.153 0.152 | 0.07 0.08 | 0.31 0.31 | sec. |
| P R Level | Deviation | M F | 0.20 0.20 | 0.0 0.0 | 2.0 2.1 | 0.28 0.27 | 0.0 0.0 | 2.0 2.1 | 0.20 0.30 | 0.0 1.8 | 2.0 1.8 | 0.34 0.33 | 0.0 0.0 | 2.0 2.0 | 0.35 0.35 | 0.0 0.0 | 3.0 2.2 | 0.32 0.31 | 0.0 0.0 | 2.0 2.2 | mm |
| | Duration | M F | 0.083 0.088 | 0.03 0.01 | 0.10 0.10 | 0.085 0.080 | 0.02 0.02 | 0.10 0.10 | 0.080 0.090 | 0.04 0.04 | 0.10 0.10 | 0.085 0.088 | 0.03 0.01 | 0.16 0.10 | 0.018 0.080 | 0.04 0.01 | 0.16 0.10 | 0.087 0.080 | 0.02 0.03 | 0.10 0.10 | sec. |
| S T Interval | Duration | M F | 0.244 0.250 | 0.14 0.10 | 0.38 0.38 | 0.25 0.23 | 0.15 0.18 | 0.30 0.30 | 0.28 0.20 | 0.17 0.30 | 0.30 0.30 | 0.27 0.20 | 0.20 0.10 | 0.36 0.30 | 0.28 0.27 | 0.22 0.20 | 0.34 0.36 | 0.26 0.26 | 0.15 0.10 | 0.30 0.37 | sec. |

AN AETIOLOGICAL CLASSIFICATION AND STUDY OF LEFT SUPRAMAMMARY PAIN OR "UPPER LEFT PARASTERNAL PAIN"

by

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A critical analysis of cases of chest pain observed by me, in private and hospital practice, during the last eight years, has revealed an amazingly high frequency or incidence of pains located in the upper part of the left chest. The present paper on Left Supramammary Pain or Upper Left Parasternal Pain constitutes but a small part of an exhaustive "Enquiry or Statistical Study into the Various Causes or Aetiological Factors concerned in the Genesis of Chest Pain in the Tropics" undertaken by me and still in the process of preparation. In order to avoid duplication of tables and figures, I have tried to present the principal framework of this paper without any reference to statistical data or tables.

Pain is "an unpleasant perception caused by sensory stimulation", its physiological existence depends on the presence of sensory end-organs and afferent fibres and tracts, its perception is dependent on the "threshold" of the individual.

The evolution of our ideas on thoracic pain or precordial pain, as related to the heart, forms interesting study. In ancient days, palpitation was the only symptom ascribed by the medical profession to the heart, heart-pain being neither described, nor mentioned, in any of the ancient scripts. As late as 1618, Albertini, in his monumental monograph on diseases of the heart, just makes a passing reference to what he terms "Cordis dolor" or "cardialgia", even this is ascribed to indigestion rather than to the heart. In spite of years of study, precordial pain continues to remain "a major clinical problem confronting the physician, at every turn, in his daily work."

Recently the subject of Left Inframammary Pain or pain in the "apical region" of the heart has been fairly exhaustively studied and published, unfortunately, the same cannot be said for pains situated in the upper region or the supramammary region of the left chest. It was mainly with a view to introduce or present this "lesser-known" type of pain that the present paper was undertaken. In my short clinical experience Left Supramammary pain has been almost as common as Left Inframammary Pain (a relative incidence of about 2 to 3).

It must be understood at the outset that the present study is entirely clinical and based upon the subjective impressions of the patient. There are no animal experiments to guide us into the realms of human sensory perception. Such a clinical study is bound to have a few flaws here and there and is likely to be tinged with the personality of the observer.

The clinical study of pain anywhere in the body is difficult. Nevertheless, considerable information can be gained about the subjective and clinical manifestations of pain by close questioning of the patient along systematic lines. Questions about pain should include, among other things

- i the exact site or localization of the pain
- ii The mode of onset and termination of the pain
- iii The duration and behaviour of the pain
- iv The character and intensity of the pain and finally
- v Associated features like "pricking pains", palpitation, vasomotor symptoms etc

An important point in practice is to distinguish precordial or chest pains of cardiac origin (*Dolor Cordis*) from similar pains of non-cardiac origin (*Dolor Pectoris*). Such a distinction though easy in theory, may prove very difficult in practice.

A word or two about the frequent use of the undesirable terms "Pseudoangina", "False angina", "Mock angina" and "Spurious angina". It was not until the time of Potain, who kept on reiterating his aphorism of "there are no false diseases, there are only false diagnoses", that these terms started dropping out of medical nomenclature. The word "Angina", however qualified, conveys to the patient a most sinister significance, a shadow of impending death or dissolution.

CLASSIFICATION OF LEFT SUPRAMAMMARY PAIN:

Pains in the Precordium are considered by Crighton Bramwell under the three headings of (1) benign types of cardiac pain, (2) grave types of cardiac pain, and (3) non-circulatory conditions causing pain in chest. Such a classification, though convenient in practice, is not comprehensive enough for our present purpose.

In the accompanying chart, I have tried to present a fairly comprehensive and convenient classification of the important forms of Left Supramammary Pain —

CLASSIFICATION OF LEFT SUPRAMAMMARY PAIN (based on personal observations)

I INTRA-THORACIC CAUSES —

i Cardiac Causes

- 1 Endocarditis
- 2 Myocarditis
- 3 Pericarditis
- 4 Valvular diseases
- 5 Cardiac strain, fatigue or overwork
- 6 Rapid heart-action
- 7 Extrasystolic pains

ii Vascular Causes

- 1 Hypertension
- 2 Arteriosclerotic heart
- 3 Angina Pectoris
- 4 Anomalous forms of coronary thrombosis
- 5 Aortitis
- 6 Aortic aneurysm
- 7 Intermittent claudication of other arteries (?) (Posselt's syndrome)

iii Non cardiovascular Intrathoracic Causes

- 1 Pleurisy and empyema
- 2 Pneumothorax
- 3 Lung diseases
- 4 Mediastinal diseases

II LOCAL LESIONS OF THE THORACIC WALL OR CAGE

(affections of the skeletal framework of the thorax)

- 1 "Precordial Indurative Panniculitis" or Cellulitis
- 2 "Generalized Adiposity of the Dercum type
- 3 Mastodynia, mastitis and other affections of the mammary gland
- 4 "Pectoralis (major or minor) strain"
- 5 Myofibrositis of chest-wall
- 6 Intercostal myalgias and muscle-cramps
- 7 "Regional Costal Periostitis"
- 8 Arthritic affections of the breast bone and ribs
- 9 Radicular and segmental pains, intercostal neuralgia and neuritis, herpes zoster, postural and other deformities of spine, neurofibromatosis
- 10 Briscoe's Syndrome (or "Triangularis Sterni Strain")

III EXTRATHORACIC AND INTRAABDOMINAL CAUSES —

- 1 Gastrogenous causes, so called "gastro-cardiac syndrome," so called "gastric cardiospasm"
- 2 Colonic distension, "Diaphragmatic flexure" syndrome
- 3 Oesophageal spasm, oesophageal herniation
- 4 Discharges of the gall bladder
- 5 "Hiatus hernia", "diaphragmatic eventration", "Diaphragmatic tic or flutter" (of Portex)

IV TOXIC CAUSES

- 1 "Tobacco Angina" "tobacco pain" etc,
- 2 Alcohol, tea, coffee, drugs, etc

V NEUROGENIC AND PSYCHOGENIC CAUSES

- 1 Neurocirculatory Asthenia
- 2 The "common heartache" or "breast ache"
- 3 "Cardio neurosis" or "functional pains"
- 4 "Cardiac Psychosis"
- 5 Precordial tenderness

VI VASOMOTOR, METABOLIC AND ENDOCRINE CAUSES

- 1 Angina Vasomotoria, (Nothnagel's syndrome)
- 2 Diabetes
- 3 Gout
- 4 Menopausal pains
- 5 Puberty
- 6 Hyperthyroidism

I INTRATHORACIC CAUSES

The intrathoracic causes of supramammary pain which are many and diverse are enumerated in the accompanying table. These causes although important are so well known to the medical profession that any detailed consideration of their genesis and modus operandi is hardly necessary. Besides, the object of the present paper is to direct attention to the lesser known forms of supramammary pain which are included in groups II, III, IV, V and VI of the accompanying table.

II LOCAL LESIONS OF THE THORACIC WALL

In my series of cases of Left Supramammary Pain this group appears to play a most important role in the causation of this symptom. There is an unfortunate tendency on the part of the majority of clinicians of today to label any precordial pain, that is not of cardiac origin, as "functional" "neurotic" or "hysterical". Such an attitude, besides doing an injustice to the patient, serves no useful purpose as it does not go down to the root-cause of the patient's trouble, the patient, who gets no sympathy from the doctor and later, even from his relatives, just has to put up with his lot until the local factor responsible for the pain is finally spotted or just remedies itself. In my experience, a large majority of precordial pains, especially left supramammary

pains, owe their inception to some local factor or factors, often within the substance of the thoracic wall itself. These so-called "topoalgias" or pains of the precordial region, secondary to local lesions of the thoracic wall, are very common indeed and usually masquerade either as "anomalous anginas" or as "cardio-neurotic pains". In any case, the treatment usually given is either inadequate, inaccurate or even harmful and the patient goes from doctor to doctor in search of relief or sympathy.

1. The so-called "Precordial cellulitis" of "anginal character", described by Vaquez and others merits our attention. I personally prefer to term this condition differently, the alternative designations of "precordial panniculitis" or better still "precordial indurative panniculitis" are suggested by me as being more scientific. Dixon designates this condition as "precordial fibrositis".

This is a fairly common and yet "little known" form of precordial pain or "topoalgia". According to Vaquez, "cases of this kind are far from unusual". It is characterized by small areas of local, painful induration under the skin. It is somewhat allied to the better known entity of the "rheumatic, indurative or nodular headache of Pollock".

The main characteristics of Precordial Panniculitis which serve to clinch the diagnosis are worth enumerating: (1) The pain is persistent, though showing exacerbations or paroxysms. (2) The pain is not substernal as a rule, it is usually to the left of the sternum. (3) No relation to exertion or food. (4) Made worse by exposure to cold and humidity. (5) Intensity increases at some definite period of the day. (6) According to Vaquez, firm pressure over the precordium with the palm of the hand evokes no pain but light pinching or picking up of the skin may evoke excruciating agony or pain in certain small or localised areas, which remain consistently painful, the other areas in close proximity appear immune to these stimuli. (7) On palpation one feels small areas of induration (? "rheumatic nodes" or swellings) the so-called "cellulitic spots of Vaquez" which are tender to touch. (8) A grating sound may be elicited while palpating the nodules.

The exact nature of this entity remains obscure. In my opinion, Vaquez's theory of origin of this entity is rather far fetched. According to him, the patient, "influenced by an unconscious suggestion to enquire into the sensitiveness of his own heart", continuously goes on palpating or exploring the precordium with his finger-tips, this exploration becomes incessant and progressively more and more energetic. As a result of the repeated traumatism, a cellulitis or cellulitic induration arises in the region of the precordium.

That repeated palpation of the precordium can result in actual cellulitis of the subcutaneous tissues appears unlikely. Would it not be more rational, in view of its close similarity to the better known entity of the "rheumatic, indurative or nodular headache of Pollock", to regard it as a mild inflammation of the subcutaneous tissues (or "panniculitis") secondary to local chilling, to trauma, to septic absorption or to a rheumatic trend? After all, it does display the other characteristics of rheumatic affections viz its aggravation at certain times of day, the palpation of tender indurative nodules and its close similarity to rheumatic headaches. In view of the above discussion, I feel justified in re-asserting that this fairly common entity of Precordial cellulitis, fibrositis, or "panniculitis" is probably of the nature of a "rheumatic

manifestation", secondary to local chilling, or septic absorption, or trauma in a person predisposed to rheumatic disorders

2 Generalised adiposity (especially of Dercum type)—In generalised, painful forms of obesity, such as occurs in Dercum's disease, local areas of fat tend to become extremely painful and tender to touch. If these tender lumps happen to involve the precordial fat, as they often do, diagnostic difficulties are likely to crop up. In the last year, I have come across two cases of this type, the maximal sites of fat-pain in Dercum's disease were located in the left supramammary regions. In both these cases, the correct diagnosis was arrived at by (i) finding similar (though less painful) nodules of pain in the other regions of the body (ii) by exploring the exact foci of pain and tenderness within the substance of the adipose tissue (iii) by excluding all the other better known causes of precordial pain and tenderness. These cases respond favourably to the administration of Thyroid and Ext. belladonna orally and to local infiltration with 2 per cent novocaine solution.

3 Affections of the Mammary Gland—It is important to remember that the entity of Mastodynia, often mentioned in surgical text-books, is not a myth but a definite entity that one has to contend with from time to time. Cases of this type are usually passed off either as "neurosis" or "pseudoangina" and left untreated. Besides gross lesions of the mammary gland such as carcinoma, tuberculous and benign tumour, there are conditions where the mammary tissue may appear practically if not quite normal and yet be the principal culprit, in the genesis of left sided (or right sided chest) pain. From my small experience, I am able to single out three main causes of "left supramammary pain" of mammary origin, viz

a Chronic Mastitis, especially Lobar Mastitis—One should make it an invariable rule to look out for tender mastitic lumps in cases of precordial pain. When noted on the right side, the patient seldom goes to the doctor, for examination, when the pain happens to be on the left side, the mind of the patient invariably wanders off to the heart and hence the visit to the doctor. These local lumps of chronic mastitis appear to be particularly common in the upper left lobe of the breast and thus tend to lead to errors of diagnosis. Points to note in diagnosis are (A) The age of the patient which may afford the clue (B) The exact localization of the site of pain which can be found by careful palpation to be within the mastitic lump (C) The co-existence of similar lumps in the opposite breast (D) By the exclusion of other causes of precordial pain (E) Response to organo-therapy.

b Premenstrual Breast Pain—This is common enough when looked for. Its frequent localization to the left side is probably explained by the fact that the pain is often of double origin, partly endocrine and partly neurotic. Anyhow, its relation to menstruation should be noted. Organotherapy may prove beneficial in this group.

c "*Mammary pull*" or the "*Mammary-drag pain*"

I am afraid I am unable to find a more suitable designation for this type of pain. This type of pain is particularly observed in the modern type of healthy young female who goes in a lot for exercises and fresh air. The contributory factors in this type of case are (A) Over indulgence in strenuous games like tennis and b on

(B) heavy or pendulous breasts (C) Refusal to employ proper supports or brassieres during such forms of violent exertion.

The diagnosis is usually suggested by the history of onset and by the dramatic response of this type of supramammary pain to corrective treatment in the form of "supportive brassieres"

4. "Pectoral strain"

This entity should be kept in mind when left supramammary pain arises somewhat suddenly after an awkward movement, after physical exhaustion and over-work or after trying to avert a fall. It results from the violent strain imposed either on the Pectoralis major or pectoralis minor muscle. Its main characteristics are as follows —(1) The clinical history of onset is often typical (2) The pain is of a continuous "aching" type, "like a bruise" (3) It lasts usually for a matter of days and is often maximal on the second or third day of the attack (4) It is increased by subjecting the affected pectoral muscle to strain or work (5) It can be localised, to the affected pectoral muscle by palpation (6) Slight swelling ("cramp-like") of the affected pectoral may be noted on palpation (7) Relief may be obtained by employing either light and even pressure or by heat (8) Pain particularly noted when movement is undertaken suddenly after a period of rest, as in lumbago (9) Often worst in the mornings after a night of rest, it tends to wear off during the day-time

One of my chronic patients, who is, I am afraid a bit of a neurotic also, has demonstrated "left pectoralis major sprain" in himself on at least four different occasions. During his attacks, the pectoral muscle definitely bulges out and remains in a stage of "cramp-like contraction" for hours or days. On the last occasion, his attack was brought on by the mere effort of arranging books within a book-rack.

7. "Regional costal periostitis" —This is yet another local or chest-wall entity to which I particularly wish to direct attention. In my small experience, this lesion has played a very significant role in the initiation of Left supramammary pain. Though its existence is often implied by the patient and perceived by the doctor himself, the latter is led away by the weight of his text-book studies, into diagnosing it as a manifestation of neurosis. In my experience cases of this type of Left supramammary pain are common enough, where the patient directs our attention to certain spindle shaped or fusiform swellings over one, two or even three ribs, usually an inch or two away from the edge of the sternum. The lower ribs may also be involved in this process of fusiform and tender enlargement. In the last six years, I have made a special study of this type of chest pain (based on well over sixty cases) and am able to enumerate certain characteristics likely to facilitate diagnosis. (1) The pain is strictly local and within the confines of the part or parts of the rib or ribs affected. In many cases the patient directs our attention to the pain by the use of one finger-tip (2) The pain is continuous and of a "dull aching" type or more often described by the patient himself as "bruise-like" or "gnawing" or "tooth-ache-like" (3) Exacerbations of pain are common after local exposure to chill, rains, humidity, etc (4) The pains are maximal in the mornings on awakening and again get worse towards evening after a day's work (5) The ribs most often affected are the 2nd, 3rd, and 4th, (in order of frequency) more often apparently on the

left side and less often the 7th and 8th. The upper ribs are usually affected about 1 to 2 inches away from the lateral sternal border while the lower ribs are usually affected "well out," somewhere between the parasternal and the anterior axillary lines (6) The pains are persistent, refractory to treatment and may last for months or years with periods of freedom (7) The local application of intense heat is likely to aggravate rather than ease the pain (8) Palpation (and sometimes inspection also) reveals a tender, smooth, moderately hard fusiform swelling of about an inch or more of one or more ribs The swelling is quite obvious and apparent both to the patient and the doctor (9) It is commoner in women than in men (in the ratio of about 2 to 1) and is commoner in the young than in the old (10) It appears to be particularly common in women who keep the upper part of the chest exposed by wearing loose-fitting or low-necked garments

The most suitable designation I can suggest for this fairly common entity is "costal periostitis" or better still "regional costal periostitis" In view of its apparent frequency and its importance as a cause of Left supramammary pain, it is only fair that in future, a closer consideration be accorded to this entity

8 Arthritic affections of the sterno-costal and costo chondral articulations

These are not even mentioned in text-books as causes of supramammary pain These lesions are usually seen in the form of tender, "bead-like," globular swellings of the small joints of the thoracic framework They are particularly frequent in subjects of gonorrhoea, syphilis, gout and rheumatism The customary therapeutic measures, employed in other forms of arthritis, are also applicable here

9 Segmental pains or radicular pains —(including intercostal neuralgias, neuritis, herpes zoster, spinal deformities, etc)

Recently an excellent monograph has been devoted entirely to the subject of segmental pains and painful syndromes by Judovich and Bates In the opinion of these authors, segmental pains of the chest often simulate the pains of visceral disease, many a patient has been subjected to medical and even operative procedures for supposedly pain of visceral organ until the somatic or radicular nature of the pain has been finally established

In this connection, the figures of Griffith are worth mentioning He analysed a series of 200 cases who came to him primarily for precordial pain and complained of their "hearts" He found that 60 cases or (30%) were merely suffering from "intercostal neuralgias"

Intercostal neuralgias of the chest are common enough when looked for In the opinion of Judovich & Bates "segmental pain and tenderness" is not a disease entity but a symptom complex which may arise from a variety of different causes *e.g.* toxic absorption, local chilling, trauma, poor posture, spinal deformities, spinal arthritis, etc

In order to simplify the diagnosis of this type of pain (in the left supramammary region), I will now enumerate its most important characteristics —(1) It is always unilateral (2) The pain is "band-like" and tends to involve entire segments (Gunther) In cardiac diseases, the pain tends to jump from segment to segment, involving several contiguous zones, without involving one complete dermatome (3) It is frequently aggravated by movements of a certain type, *e.g.* bending, stooping, hyperextensions of spine, etc, (4) It may be aggravated

by, but not initiated by exertion (5) It is often aggravated by coughing, sneezing and other factors which tend to suddenly raise the intra-thoracic or intra-abdominal tension (6) It does not disappear at rest (7) According to Judovich & Bates, local "tenderness" is the most important single feature of this type of pain The tenderness is not uniform in its distribution but is usually maximal at the points of exit of the branches of the intercostal nerves The commonest sites of tenderness are the paravertebral area corresponding to the posterior primary division, the mid-axillary region at the site of exit of the lateral cutaneous branch and most of all, near the costo-sternal articulation, at the point of exit of the anterior cutaneous branch In some cases, the tenderness is restricted to the exit-point of the anterior cutaneous branch only Superficial and deep forms of tenderness can both be elicited, the former by pinching or pricking the skin, the latter by pressing the skin firmly against a muscle or bony structure (8) There is usually no radiation into the arm (9) Its site of origin is never retrosternal (10) Diathermy and infiltration of the tender areas with 2% novocaine or procaine may afford dramatic relief for months or years

The syndrome of Lian and Boyer

This is a condition of combined left inter-costal and brachial neuralgia first described by Lian of Paris and later by Boyer, his pupil It may cause extreme suffering to the poor patient and may be indistinguishable in every way from the much more common Angina Pectoris of Herberden

Herpes Zoster —The radicular or segmental pains of Herpes Zoster may involve the upper left chest and unless the skin lesions or scars are spotted, the condition is likely to be taken for simple inter-costal neuralgia or even for Angina Pectoris Crighton Bramwell, in his treatise on diseases of the heart, cites the case of a well-known physician who regarded himself as a case of classical angina pectoris in the pre-eruptive phase of Herpes Zoster

Recently, we witnessed at the Parsee General Hospital post-herpetic pain confined to the Left supramammary pain It was the history of an antecedent skin lesion and the presence of unilateral areas of pigmentation that clinched the correct diagnosis in this case

The Edgar Cyriax Syndrome —Cyriax has described upper left chest pain (so-called pseudo-angina) as the result of being very "round-shouldered" from habit In his cases, excellent results were claimed with "cervicodorsal mobilization" of the otherwise "practically immobile" spine in cases of this type

Intercostal neuralgias of aortic origin —

In luetic aortitis and in syphilitic aneurysms of the aorta, inter-costal neuralgias often arise, probably as the result of pressure In February 1946, I had the opportunity of observing two cases of aortic aneurysm both with severe segmental or radicular types of pain in the upper left chest and both in the very same house! What is more these two patients, who happened to be neighbours, died in the very same week!

III INTRA-ABDOMINAL CAUSES OF LEFT SUPRAMAMMARY PAIN

(1) *Of gastrogenous origin* —

This type of precordial pain has been described under many designations It has variously been termed "Gastrocardiac syndrome,"

"gastrogenous angina," "mechanical abdomino-cardiac distress (of Herrmann)" The majority of authors are agreed that at times, pain in the precordium, either inframammary or supramammary, arise as the direct result of excessive gaseous distension or flatulence of the stomach. Herrmann goes far enough to assert that abdominal gaseous distension constitutes the commonest cause of benign or non-specific thoracic pain. According to him, the chest pain is probably caused by the abdominal distension forcing the diaphragm up into the chest, by the lifting of the cardiac apex which normally rests on the cupola of the diaphragm and by the rotation or twisting of the heart on its longitudinal axis. It is difficult to decide whether the chest-pain in these cases is due to the actual contact of the uplifted heart against a sensitive chest wall or to embarrassment of the coronary arterial flow as the result of the rotation of the heart on its long axis or again to stretching or tension of the peritoneum over the distended stomach (Herrmann).

The main characteristics of this so-called "*gastro-cardiac syndrome*" or symptom complex are as follows: (1) As stressed by Vaquez, it is more in the nature of a sensation of weight or vague aching in the precordium rather than actual pain. (2) In many cases, there is associated discomfort or pain in the region of the stomach bubble just above the left costal margin, with a feeling of distension or "bursting." (3) It is often related to the ingestion of heavy meals, gas-producing foods or effervescent drinks. (4) The fixedness or constancy of the pain may be striking. (5) There is no radiation of the pain in any direction. (6) Percussion reveals a "drum-like" or tympanitic note, fairly extensive, above the left costal margin. (7) Relief from belching, change of posture, carminatives and gas absorbers. (8) Fluoroscopy shows a high diaphragm with a huge "gas-bubble" in the stomach. (9) The pain can be reproduced in the patient by the administration of an effervescent mixture or powders. This was observed by me on numerous occasions, when investigating the effects of artificial gaseous distension of the stomach on the deflections of the Electro-cardiogram at the J. J. Hospital.

2 *Of colonic origin* —According to Herrmann "segmental distension" of the colon, proximal to spastic constriction may cause referred pain in the left upper thorax. The same mechanism is probably concerned in cases of precordial pain or ache noted by patients of spastic constipation, during acute phases of their malady.

Of late, the "diaphragmatic flexure syndrome" of Kauter has been attracting the attention both of cardiologists and gastro-enterologists. By the term "diaphragmatic flexure," Kauter implies a splenic flexure (roentgenologically proved) located just under the left cupola of the diaphragm, this is said to occur in 15% of normal people. This anatomical anomaly is not associated with symptoms unless accompanied by some associated condition like "gas production" due to colonic malfunction.

The most important symptoms of this condition are heart-burn, thoracic distress and cardiac embarrassment. Heart disease may be simulated. Treatment of this condition must include effective colonic evacuation.

3 *Of oesophageal origin* —Jackson & Jackson, in 1936, went so far as to contend that Angina Pectoris is due not to coronary or

aortic disease but to "acute spasmodic unco-ordinated contractions" of the oesophagus and stomach

In support of their theory they mention the frequent association of cardiospasm with angina, the presence of gas in the stomach with relief from belching, etc. This theory has been attacked and more or less disproved by Paul White

"Oesophageal herniation" —According to Herrmann, in no other condition is Angina pectoris more closely simulated or mimicked than in cases of "oesophageal herniation"

4 *Of gall-bladder origin* —The relation of gall-bladder disease to heart-pain has been put on a firm footing of late. That lesions of the coronary arteries are particularly frequent in cases of gall-bladder infection is now common knowledge. This subject does not, however, concern us here as the type of heart pain witnessed in these cases does not belong to the category of Left supramammary pain

5 *Of diaphragmatic origin* "Diaphragmatic hernias" or "Hiatus hernias" may give rise either to upper left thoracic or to substernal pains of anginoid type. This type of pain is (1) induced by drinking or eating (2) bears no relation to exertion and is (3) diagnosed by the use of the Roentgen ray

In several cases of "diaphragmatic eventration" that I have had the opportunity to observe, thoracic pains have been frequent enough. Both inframammary and supramammary pains on the left side, are complained of, periodically, by these patients, especially after heavy meals, alcoholic bouts and during attacks of gastric flatulence

The condition of "Diaphragmatic Tic" or "Flutter" described in 1936 by Porter, should be kept in mind, particularly as it tends to simulate the dread condition of Angina pectoris

IV TOXIC CAUSES OF LEFT SUPRAMAMMARY PAIN

The so called "Tobacco Angina"

Within the last few decades an enormous amount of literature has accumulated on the subject of Tobacco Angina. In spite of several hundred papers published on this subject our knowledge remains, to this day controversial, fragmentary and disseminated.

On the one hand, authorities like Clifford Allbutt and Huchard have described severe forms Angina which they attribute to tobacco, Huchard went far enough to distinguish several distinct Varieties of Tobacco Angina. On the other hand, there are authorities like Brooks, who deny the very existence of the entity of tobacco angina

The present-day view is that the production of cardiac symptoms in cases of tobacco smoking or chewing is entirely a matter of "relative individual susceptibility". Individuals can roughly be classed into two main groups, in relation to tobacco viz (1) "those who are sensitive" or susceptible to tobacco even when the latter is administered in minute amounts, as described by Moschowitz and others and (2) those who can tolerate enormous amounts "without turning even a hair"

The recent work of Harkavy has served to confirm the general impression that the cardiovascular system is particularly vulnerable to the ravages of tobacco, especially when the associated disease happens to be Thrombo-angitis obliterans or coronary artery disease

According to Brooks, the precordial pains of tobacco can be distinguished from those of genuine heart-pain by attention to the following details (1) Tobacco pains are seldom as sharp as those of Angina (2)

Tobacco pains are not well localised as a rule (3) Tobacco angina is usually more persistent (4) Tobacco pains are usually of the nature of "dull heavy aches" (5) Tobacco pains are seldom referred to the left arm or elsewhere.

NEUROGENIC AND PSYCHOGENIC CAUSES OF L S PAIN

(1) *Neurocirculatory Asthenia* (the so-called "effort syndrome," "Irritable heart," "D A H" "disordered action of the heart," "Soldier's Heart" or "DaCosta's Syndrome")

This important entity was first brought to the attention of the medical profession during the great war of 1914-1918. Since that time, it has continued to engage the attention and time of numerous cardiologists of repute. In spite of these extensive researches, the condition—its aetiology, its clinical masquerades and its treatment still remains shrouded in mystery. Crighton Bramwell regards neuro-circulatory asthenia as a sort of benign condition characterized by an excessive response to exertion or effort of the circulatory and respiratory systems. Even gentle exercise may evoke severe dyspnoea, palpitation, faintness and precordial pain in such individuals.

Paul White prefers to regard "Neurocirculatory asthenia" as the cardio-vascular counterpart of the syndrome of Neuresthenia, where the main brunt of the condition happens to fall on the circulatory system. It is characterized by a "sort of excessive irritability and fatigability" of the central nervous system.

Certain types of individuals, apparently "in the pink of health," when subjected to the active and strenuous life of the army, seem to "crack up" completely and develop this disorder especially when they come from sedentary peace-time occupations. It is important to realize that this condition, common in soldiers, may also occur fairly frequently in civilians and peace-time workers, the condition may arise either "de novo" in perfectly normal individuals or is superimposed on top of some basic cardiovascular disease or disorder.

It is said that whilst about 20 to 30% of all cases of Neurocirculatory asthenia have organic heart disease as well, about 5% (approximately) of all cases of organic heart disease show the co-existence of neuro-circulatory asthenia, the latter is found particularly in cases of rheumatic heart, coronary heart and hypertensive heart (in that order). In my series of private cases, the incidence of neuro-circulatory asthenia in organic heart cases has been much higher.

Type of Pain There is a characteristic "heart ache" or precordial pain, "a dull heavy ache" in the left breast, lasting for hours or even days, with intermissions and relapses, often associated with palpitation and suspirous or sighing respiration and occasionally with radiation into the left arm. Sharp, stabbing pain are often associated, precordial tenderness, hyperaesthesia or hyperalgesia are noted in about 50% of the cases (Meakins & Gunson).

(2) The "Common Heart ache," "precordial ache" or "the common heartache of fancy and of fact" (P. White). This was originally classed as "simple fatigue pain" by White & Wood and regarded as a symptom of myocardial fatigue or exhaustion, after further years of study of this type of pain, Paul White now prefers to regard it as a sort of "nervous heart pain." According to this author, it is the commonest type of cardiac pain, occurring with much greater frequency in non-cardiacs than in cardiacs. Important factors concerned in its

production are (i) A hypersensitive nervous system, this is considered an essential ingredient of this type of pain (ii) Either general debility and exhaustion affecting the individual as a whole or else a fatigue or exhaustion of the myocardium itself. Individuals who are "down in body and mind" and those with forcibly overacting hearts as in hypertension, are particularly prone to develop this form of chest pain (iii) The larger the heart, the more forceful its action,—the greater the likelihood of getting precordial ache, it does however, occur quite frequently in the presence of perfectly normal hearts, both in point of size and action.

It displays the following main characteristics (1) It is persistent (2) comes on not during but sometime after exertion (3) Usually worst in the afternoons and evenings and may even extend into the early part of the night (4) It is very common in women, especially at the climacteric (5) It is frequently accompanied by other symptoms like sighing, flushings, faintness, tremors, hyperaesthesia of the precordium, etc (6) Very resistant to treatment (7) The ultimate outlook is good, according to Doris Baker.

The pain of precordial ache is ascribed to the impact of the heart-apex against a sensitive chest-wall, "the stimulus accumulates until it reaches the threshold of consciousness when the preceptive nervous mechanism is hypersensitive" (Bramwell).

(8) Cardiac Neurosis or Functional cardiac Pain or psychoneurotic precordial pain.

According to Yaskin, whilst in "Cardiac psychosis" symptoms develop in the course of or are causally related to organic heart disease, in "cardiac neurosis" (on the other hand) symptoms develop without any primary cardiac disease.

In Yaskin's opinion, cardiac symptoms somewhat differ in the different types of Neurosis, of which the principal types are the following viz (1) Anxiety neurosis (2) Conversion hysteria (3) Anxiety hysteria (4) Compulsive-obsessive Reactions or the Psychasthenia of Janet (5) Neuresthenia.

The pain of cardiac neurosis has no organic basis at all, it is secondary to "psychogenic" factors. The patient gets the initial suggestion or idea from a physician who suggests the possibility of cardiac disorder, or from a relative or friend—the subject of heart-disease or from newspaper cuttings or from a stray perusal of medical journals. In any case, this initial suggestion is stored up, nurtured and finally built up by the patient into a "full-blown" neurosis with precordial pains and all.

Psychoneurotic precordial pain is difficult to describe as it displays an infinite variety, not only in different patients but even in the same patient from time to time. Some of its main characteristics or attributes are (1) Inconstancy is probably its greatest attribute, the pain tends to vary from day to day in intensity, localization and character, the same patient may complain of a cramp-like pain on the first day, a burning heat on the second day and a feeling of "void" or emptiness on the third day (2) The pain factor is nearly always exaggerated or described in "superlatives" "hyperbole", it is often described as "unbearable," "excruciating," "devastating" or "agonizing" by the patient (3) According to Bramwell, a point of importance to note in these cases is that there is no fixed or constant threshold of

pain On some days, even with violent exertion, there is no discomfort at all, whilst, on other days a trivial movement (like stooping) or a minor exertion (like a short walk) may precipitate a violent attack of pain (4) It is usually atypical as regards onset, character, duration and distribution and does not conform to the "Anginal model" (5) It is nearly always asymmetrical or left sided, unlike angina which tends to be central or substernal (6) It gets worse when the patient is fatigued, annoyed or emotionally upset (7) It is often relieved by diversion of the mind or reassurance (8) Often worse in the mornings and again in the afternoons (9) There are usually symptoms of depression, lack of concentration, inattention, introspection, fatigue or insomnia (10) A "fear of going to sleep" is rather characteristic (11) Tends to become worse in cinema-houses, stuffy halls and in ill-ventilated rooms (12) The patient has usually no occupation in life except perhaps the "dragging out of a blase or unhappy existence" (13) Feelings of "Vacancy," "emptiness" or "void" are frequently described in the chest, the patient feels "as if the heart is not in its place at all" or "as if the heart has turned into jelly" (14) According to Scherf & Boyd, there is usually a parasternal spot of pain and tenderness at the attachment of the third left rib, they find this is a common feature of neurosis, especially sexual neurosis, hence a tactful enquiry into the sex-life of the individual is considered necessary by these authors in cases of this type

4 "Precordial tenderness" —Unfortunately, owing to Mackenzie's pioneer work on the subjects of "referred pain" and "viscero-sensory reflexes," the medical profession was swayed for years into regarding this symptom as a definite indication of underlying cardiac pathology At the present time, the pendulum has swung to the other extreme and authorities are wont to regard this symptom as being invariably functional—a sign of a "sensitive chestwall in a nervous individual" This may be so in a large number of cases but there are exceptions, for instance "local foci" of precordial tenderness, when investigated properly, may unravel the true cause of the precordial pain as being of "thoracic-wall origin", for instance, local conditions like Regional costal periostitis, intercostal or segmental neuralgia, myalgia and panniculitis, may be first brought to the notice of the clinician by the discovery of these tender foci .

VI MISCELLANEOUS CAUSES

"Angina Vasomotoria" (Vasomotor Angina), "Nothnagels" syndrome, or the "Episnode of Pal"

This type of pain, frequently in young subjects of "Spasmogenic habitus," displays a dramatic onset and a characteristic clinical picture

It is said to be caused by a "storm of sympathetic vasomotor impulses" augmenting the action of the heart According to Sir Thomas Lewis, the chest pain, in these cases is of muscular origin and due the liberation of a P substance

The clinical picture is often characteristic (1) Usually observed in young neurotics (2) especially after exposure to chills or alcoholic bouts (3) There is usually "pressure-pain" or "precordial oppression" in the left breast (4) Alterations in the rate of the pulse and in

the level of the blood pressure are common (5) Sharp submammary twinges of pain are often associated (6) Flushing of the skin, cold sweats, throbbing sensations, cold extremities etc., from an integral part of the clinical picture (7) Sensations of suffocation, choking, and fullness of the neck are particularly frequent (8) Slow injections of Histamine 1 mg often afford dramatic relief to these cases

TREATMENT OF LEFT SUPRAMAMMARY PAINS

The treatment of a heterogeneous entity (of diverse aetiology) like "chest pain" is necessarily a difficult matter for discussion, it involves not only the science but the art of Medicine. In the case of Left supramammary pain, any such discussion of treatment proves doubly difficult for the following reasons (1) First and foremost, our knowledge of this entity is fragmentary and controversial. Substernal pains and inframammary pains have received the attention of practising physicians for the past two centuries or more but the same cannot be said for "supramammary pain" which hardly receives a mention in the standard text books of medicine or cardiology (2) The second reason, why treatment is so difficult in these cases is that the aetiological factors responsible for the genesis of this entity are literally "myriad", there are causes not only *within* the thoracic cage but also in the thoracic wall itself and even within the abdominal cavity. Success in treatment will therefore depend upon a proper and painstaking appraisal of the root-cause or causes of such pain. In this connection, it should be noted that every few years new causes of supramammary pain come to light, in medical literature. Unless and until our knowledge of this entity becomes complete and comprehensive, our success in therapeutics will necessarily remain partial (3) In practically all cases of long-standing Precordial pain, treatment will have to be directed both to the "psyche" and the "soma" of the individual, these two elements, which are closely interwoven or "knitted together" in any given case, require proper analysis before the start of any form of rational therapy.

The first essential in the treatment of any Left supramammary pain is to determine the aetiological factor or factors concerned in the genesis of that pain, the next essential is to determine the exact roles of the "psyche" and "soma" in the genesis of that pain, finally any therapeutic measure or measures applied should be "individualized," according to the exact needs or indications of the given patient. In this connection I would like to repeat a few words of advice on rational treatment, from the pen of Walter Hamburger (somewhat modified) as they apply with added force to the subject of Left Supramammary pain (1) The treatment must be based upon accurate diagnosis, which in turn depends on a careful and painstaking study and analysis (2) It must be up-to-date and abreast of the times (3) It must be individualized to fit the particular patient and not merely his diseases, any treatment, on the "rule of the thumb principle" should be discarded as irrational (4) It must be elastic and resourceful (5) It should encompass the whole mental and emotional make-up of the patient (6) It should attempt to deal not merely with the presenting symptoms or symptoms but, most of all, with the underlying disease-process or lesion (7) Finally, it should take into consideration the environment, the financial resources and even the friends and relatives of the patient

SUMMARY

The paper presented, herewith, on the subject of Left Supramammary Pain claims to introduce into medical literature the following new conceptions or ideas (1) That Left Supramammary Pain is not a clinical entity but a symptom-complex or syndrome that arises from a host of different causes, classified, in this paper, under the captions of Intrathoracic, Thoracic, Extrathoracic, Metabolic, and Psychogenic causes. Clinical descriptions are attempted of the various aetiological types of Left Supramammary pain in order to facilitate their differential diagnosis. (2) It serves to remind us that the majority of Left Supramammary pains are of extra-cardiac origin, organic diseases of the heart account for but a minority of all cases. (3) In our experience the root cause or basic cause in the majority of such cases, lies not within the thorax but actually in the framework of the thoracic wall itself. In this connection, the reader's attention is particularly drawn to the following interesting syndromes of pain viz "precordial indurative panniculitis," "regional costal periostitis," "segmental and radicular neuralgias," "pectoral sprain" and "mastodynias." (4) In the literature of today, on the subject of chest pains, there is a tendency to accord the "lion's share of attention" to the "psyche" of the individual with complete neglect of the "soma." Every pain, that fails to conform to the traditional description of angina pectoris is promptly regarded as being "functional," "neurotic" or "psychogenic," without even " cursory investigation of the chest wall in order to exclude local causes or somatic causes of pain. Such an attitude is reprehensible on the grounds, that besides being inadequate, it fails to determine the root-cause of the pain and yields little or no therapeutic relief to the patient. (5) By insisting on "individualization" or "rationalization" in the treatment of Left supra-mammary pain, it hopes to bring relief to at least a few of its unhappy victims. (6) Last, but not the least, it presents, for the first time, a comprehensive classification of the causes of Left supramammary pain, along aetiological channels.

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TUBERCULOSIS OF BONES AND JOINTS

OPEN AIR TREATMENT AT VERSOVA—A REVIEW OF RESULTS

by

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In India there are no special hospitals for tuberculosis of the bones and joints. The average case is put in a plaster of paris or some sort of a splint and treated at home or sent away to his native place where a few recover and majority die. This paper has been presented primarily to show what an open air treatment can do to a case of tuberculosis of the bones and joints. In all civilized countries these cases are treated in special hospitals far away from the crowded cities in the open air. The first movement of treating these cases by the open air started in Liverpool and the rest of the world followed the example of Liverpool rapidly when they were convinced of the value of treatment in an open air hospital. In India, so far no attempt has been made to develop this. Firstly, due to foreign domination, and secondly, due to poverty and ignorance such a treatment was not undertaken so far. The general surgeon is used to rapid operations and quick cures. By nature, he cannot develop that patience which is necessary for these diseases. With the coming of Orthopaedic surgery these hospitals are bound to develop. They require a specialist who can devote time and can have interest to look after the same patient for years for a very small remuneration.

It was Hugh Owen Thomas (1834-91) who realised the value of open air in tuberculosis of bones. He used to insist on even his poor patients being kept outside in the open air. He used to visit them frequently and saw them improving. It was a common sight in his days to see children on their frames lying outside in the garden or on the street. His nephew, Sir Robert Jones (1858-1933) had the genius to appreciate what cured these cases. He found luckily in Miss Agnes Hunt, one of his patients, an admirable worker, who first started a small hospital in the form of small shades at Baschurch (England). From these beginnings by the efforts of Sir Robert Jones and Miss Agnes Hunt that hospital has grown today to a hospital of 1500 beds devoted mainly to this problem. People from the world came to see this experiment and went back convinced of the treatment of tuberculosis of bone in open air.

Untreated tuberculosis gives rise to crippling in children and in adults. Sir Robert Jones says "The cripple has always presented a problem awaiting solution, and his story is unequalled in its tragic sequence of obloquy and neglect. In ancient days he (cripple) was the embodiment of magic, and in mediæval times had fallen to the estate of public mockery and reached his highest ambitions as the King's Jester. When raised by rank above the derision or contempt of the mob, he

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earned a reputation for malice, cruelty, and perversion. The dwarf became the symbol of all the evil that trades upon the credulity of the race. Again in a later period the cripple was frowned upon as an outcast and crawled through his miserable distorted life as an example of divine punishment and humiliation.

"Unfortunately, although oppression passed away, an even more damaging state of affairs took its place. The prospects of the cripple were threatened no longer by public hostility but by the congestion of industrial life. Whatever virtues, our civilization may have produced, it has concentrated labouring people in conditions so restricted and so abnormal that deformity has evolved as surely as ague from a swamp. Now a rising percentage of cripples has grown to manhood uncured and even untreated and become the national problem that faces us today. That the medical profession has striven conscientiously to prove treatment for the cripple is beyond question, but until recently the most elementary were but rarely recognised and hospitals devoted to the care of crippled children stood in the heart of cities little better than hot beds of infection. Upto this point the history of the cripple had been one of the most poignant pages in human life."

"It was at this stage that certain profoundly important changes were marked in the public conscience. The tendency towards a more healthy existence marked the end of the nineteenth century. The great development of orthopaedic surgery became more and more a common place. Finally the war broke out with terrible swiftness and proximity to our homes. For the first time thousands of British women were brought into contact with physical agony and mutilation, and with the prospects of permanently crippled men. Numerous hospitals of the simplest character were erected, and exposed to sunlight, wind and weather. In a word, the lesson was grasped by the civilised world that health is strengthened and not endangered by fresh air, that modern surgery can achieve miracles of reconstruction, and that the cripple by his fine courage and endurance can become a source of spiritual pride and envy to the strong."

"But long before the war the first great pioneer effort had been accomplished under the definite inspiration not of treatment but of cure, and out of this had developed a practical organization of professional and voluntary work. A brief outline of this organization will serve to show the tendencies and the ideals. To follow these early struggles is to realise that out of the enthusiasm of a handful of workers not only has there grown up a definite and highly organised movement, but that the next and finest chapter must mean the national action that will treat the cripple child as the result of a preventable catastrophe and not a visitation from the hand of God."

"Over twenty years ago with the help and inspiration of Miss Hunt, the first really open air hospital was established at Bascureh, in Shropshire. Its early days were days of hardship, but never of despair. The hospital was composed of few sheds in a field, the operating theatre occupied the back kitchen, and obstacles were so frequent and so apparently unsmountable that they ceased to raise a qualm and became indeed an exhilarating part of the daily routine. Around Miss Hunt gathered a body of enthusiastic young women who became in due course experts in the application of splint and plaster work. But the great lesson of Bascureh was the benefit of exposure to the open

air night and day The second lesson was the importance of efficient orthopaedic training for the nursing and after care staff "

Today for the poor patients there is no arrangement in the whole of India It is one of the duties of the Government to provide facilities for these poor Even when tuberculosis affects the rich, majority of them are put in a plaster or in a splint and treated at home in a congested city in dark room In a few months they get disgusted with the plaster and lying down How far they lie down is also doubtful Some of them whose disease is mild or early or have a better resistance get well, but those in whom it is more severe, die after a few years Their relatives feel that they have done all that was necessary but the patient had no luck Gentlemen, I feel majority of these could have been benefited if kept in an open air hospital Of course open air alone is not enough In places like Talegaon and Panchagani the air is excellent but it is difficult to get a surgeon to look after them there At Versova I have tried to get both the open air and a surgeon to look after them Mercer in 1946 in discussing prognosis of tuberculosis of bones and joints in his text book writes that "reference should be made to the great improvement in prognosis that has attended the efficient sanatorium regime now practically universal in this country " This shows the importance of open air in prognosis of tuberculosis of bones and joints In these hospitals besides the open air there is a peculiar buoyant atmosphere The psychological part of seeing one of them going out cured is a tonic which patients at home can never get The patients are also at various stages of improvement and this helps a new patient considerably, in bearing the tedious time he has to pass lying down If treated at home, he soon gets bored and becomes a nuisance to himself and to his near relatives I do not mean that all die if treated at home, but certain I am, that more people live and do well when they are treated in an open air hospital

At Versova these patients are kept entirely in the veranda day and night (for 24 hours), even on the coldest day Every week they seem to be improving All are given both general and local treatment of some sort in a plaster or in a splint They are given colloidal calcium with vitamin 'D' injection 2 c c every day and a mixture or syrup containing Iron and Arsenic and Glycerophosphates, Tuberculin in very minute doses 1/1,000,000 has also been given to all these cases once a week gradually increasing to 1/10,000 Sedimentation rate is done as a routine by Westergren's method, and shows improvement with the clinical progress Both rest and open air help them to improve Out of these open air is more important in my opinion as can be seen in the case No 17 The patient had no rest while at Vasai, but took a lot of nourishing food and she has improved in spite of no rest One must have known of many cases which have gone down in spite of rest in plaster So it is necessary to combine both rest and open air Cod liver oil, calcium, vitamin D, ultra violet and solarium are all adjuvants But often they are used as the primary treatment

Case 1 Master H aged 11, admitted on 22-6-45 On admission he had bilateral tuberculosis of the ankles for the last seven years He was treated in various places in Sind and Bombay He was advised bilateral amputation of the leg On admission he had multiple sinuses on the left side which was the worse side and the ankle had swollen three times the normal size X ray of the foot showed very great decalcification and trabeculations had disappeared The ankle on the right side was not as bad as that on the left side His sedimentation rate was 100 mm per hour The

patient was getting 101°F temperature. He was put in plaster above the knee and was given penicillin 5000 units 3 hourly for 2 months for controlling the secondary infection. The discharge became less by penicillin but sinuses could not be cured. X-ray after one year showed that recalcification had started. After one and a half years—in February 1947, a crash splint was given and the foot dropped gradually disappeared. Now the sinuses have healed and the X-rays show very great recalcification and trabeculations. The patient is also looking quite healthy and normal.

Case 2 Mrs K aged 25, was admitted on 9-5-44. She had a very acute tuberculosis of the left elbow and she was very much emaciated. She had massaged the elbow vigorously and sinuses developed two months after the starting of the disease. The elbow had swollen to almost twice the normal size. She was asked by a surgeon to get it amputated. On admission her temperature was 101°F. She was then plastered and given the usual treatment. Temperature settled down in three months and so she went to Jalgaon for Divali. There another surgeon advised her to get it amputated and so she hurried back to Versova and stayed there till 10-10-45 when all the sinuses had healed and the X-ray showed fused elbow. Her first X-ray showed extensive destruction of the elbow joint and severe decalcification. After five months the X-ray showed a lot of periosteal new bone formation. The latest X-ray showed bony fusion of the elbow.

Case 3 A B a boy aged 4, was admitted on 14-8-45 with tuberculosis of the right hip with a sinus on the right side. His X-ray on admission showed destruction of the hip joint and decalcification with the head of the femur trying to come out. He was put in plaster spica for two years. On 15-3-47 his hip joint showed healing of tuberculosis and the sinus also has healed. He will require fusion when he will be thirteen years old.

Case 4 Mrs D aged 50, was admitted on 20-3-45 for tuberculosis of the left ankle. She had a sinus on the outer side. She had no temperature and her X-ray showed some decalcification. Her sedimentation rate was 90 mm per hour, on admission. Now it is 10 mm per hour. She was in plaster and treated till 1-1-46. On discharge her sinus had healed and the X-ray showed recalcification. She was not been seen for the last eighteen months and now is getting an equinus deformity for which a tenotomy is suggested.

Case 5 R G male aged 47, admitted on 11-2-47. On admission he had tuberculosis of the right ankle joint with three sinuses. He was advised to get his leg amputated at the beginning but refused to get it done. He was seen after one year of the disease when he was ready to get it amputated. On admission his sedimentation rate was 60 mm per hour. A crash splint and usual treatment was given to him. The sinuses healed in two months and he improved very rapidly. He has been discharged with a walking calliper with which he can walk about. His sedimentation rate now is only 15 mm per hour.

Case 6 S G female 21, was admitted on 24-2-46. On admission she had a swollen left knee joint with sinuses. It was obviously tuberculosis. Her sedimentation rate was 18 mm per hour. She was given a plaster till Feb 47. She had not improved very much during this time and sinuses still persisted. The temperature settled down to normal in three months time. After February 47, a Thomas knee splint was given. The improvement since then has been remarkable and she has put on 20 lbs in the last six months. In my opinion Thomas splint mobilises the knee better than a plaster as the muscles relax, as there is no sudden jerk which is very common in a plaster. Thomas, it may be mentioned here, originally used this splint for tuberculosis of the knee.

Case 7 T C H male aged 45, admitted on 4-5-45 with quadriplegia of 3 weeks duration. He had a temperature of 100°F and sedimentation rate was 90 mm. His lesion was at the cervical fifth and sixth vertebra with dislocation and his X-ray showed destruction and decalcification. A Minerva plaster was applied. It took three months to get rid of the paralysis and temperature. He steadily improved and was discharged on 1-6-45 with a support. He took three months rest at home and since then he is doing a full eight hours duty. His lesion has healed as there is bony fusion of cervical fifth and sixth vertebra. Sedimentation rate is now 10 mm per hour.

Case 8 S P female aged 20, admitted on 13-6-44 with a lesion at second, third and fourth, lumbar vertebra with abscesses on both sides. Her general condition was very poor. A half shell plaster was given. Her temperature was 99.5°F and sedimentation rate was 105 mm per hour. She was discharged on 1-11-45 with spinal jacket. Her sedimentation rate is 15 mm per hour and X-ray shows bony fusion of the three vertebrae of course in Kyphosis.

Case 9 J F female aged, 30, admitted on 20-9-44 with lumbar abscess on the left side. It increased inspite of a plaster jacket. Her temperature was 100°F sedimentation rate 120 mm per hour. She was aspirated thrice still it increased. So it was deliberately opened as advised by Girdlestone (1944). The abscess healed in five months time and she was discharged on 15-3-45 with a belt. This rapid healing of the lumbar abscess was due to deliberate opening and antiseptic dressing.

Case 10 N A S male aged 40, admitted on 13-12-44. He had lesion of fourth and fifth lumbar vertebra. He was treated by a Taylors brace for one year. His temperature on admission was 99.5°F and sedimentation rate was 90 mm per hour. A plaster shell was given. His relatives took him to Bangalore in May 45, but there after two months he found that it would be best to return to Versova. Here he stayed till 12-2-46 when he was discharged wearing a spinal jacket. He is now doing a professional job. His X ray shows a complete bony fusion and his sedimentation rate is 5 mm per hour.

Case 11 H female aged 35, was admitted on 23-8-45 with paraplegia and incontinence of urine. Her temperature was 100°F and sedimentation rate was 95 mm per hour. Her lesion was at the eleventh and twelfth dorsal vertebra. It took four months before she could move both her legs completely. She was discharged on 1-3-46 with a belt. She has no weakness of the leg and her sedimentation rate is 20 mm per hour. She is doing all her household work.

Case 12 K P girl aged 13, admitted on 7-2-45 with a kyphosis of second and third lumbar vertebra. She was thin emaciated girl with a temperature of 100°F and sedimentation rate was 60 mm per hour. X ray showed destruction of the disc between second and third lumbar vertebra. She was discharged on 10-2-46 with a belt. Her X ray shows a complete bony fusion and her sedimentation rate is 5 mm per hour.

Case 13 V K L Male aged 40, admitted on 14-0-45 for lesion third and fourth lumbar vertebra. Prior to admission at Versova a bone graft was done from twelfth dorsal vertebra to fifth vertebra in June 43 in another hospital. On admission he had no temperature and his sedimentation rate was 30 mm per hour. He was discharged on 14-4-46. He was given a belt. The bone graft broke with a noise in December 1946. He was again kept in bed for three months and now he is free from symptoms. The early bonegrafting has not lessened his time of lying down in bed.

Case 14 H J male aged 40, admitted on 8-4-45 with lesion of twelfth dorsal vertebra. He improved in the beginning but died on 1-3-46 of severe anaemia, in spite of Liver injections and two blood transfusions.

Case 15 C female aged 35, was treated for one year and six months in another hospital. She was admitted on 15-10-45 with a sinus in the left groin and lesion of second and third lumbar vertebra. Her temperature was 99.5°F and sedimentation rate was 85 mm per hour. The sinus healed in eight months and her temperature came to normal. To-day she can walk about with a posterior support. Her sedimentation rate is now 20 mm per hour and X-ray shows lot of sclerosis.

Case 16 B male aged 14, had an old tuberculosis of the fifth and sixth dorsal vertebra for many years which has healed by a kyphosis and he was walking about. He was admitted on 10-0-47 with weakness of the legs for two weeks. He was put in plaster and this delayed onset paraplegia fortunately recovered in two months time.

Case 17 C B female aged 30, had pain in the back and a kyphosis of second and third lumbar vertebra. She was living in her home at Vasai in open air and has never taken rest. In spite of that she improved and her recent X-ray showed that the lesion is healing. She has been given a posterior support. Her sedimentation rate is 30 mm per hour.

CONCLUSION

Seventeen cases of tuberculosis of bones and joints which were treated by open air method in conjunction with other routine treatment, are presented. The results are encouraging. A plea for open air treatment of tuberculosis of bones and joints in India is made.

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Critical Notes and Abstracts

VIT K IN ACUTE CORONARY OCCLUSION Doles treated 58 patients, 40 men and 18 women between the ages of 39 and 78 years, with acute coronary occlusion, with vitamin K. The acute coronary occlusions in these patients were all associated with hypoprothrombinemia of various degrees, it was the basis for the rationale of this treatment. The amount of vitamin K usually given is from 50 to 72 mg every six to eight hours by the intramuscular and intravenous routes until the prothrombin reaches 100 per cent of normal. The number of inadequately treated patients who died was 3. Two of the 55 adequately treated patients died, this gives a mortality rate among the latter of 3.6 per cent. In 53 patients the pain of acute coronary occlusion was controlled within twenty-four hours and a normal recovery followed. Fifty-two have been able to pursue their original occupations. Not any of these patients complain of pain or show any evidence of decompensation. The blood pressures have maintained the same level as before the attack. The prothrombin times average 98 per cent of normal. The fact that pain remained absent as long as the prothrombin was above 70 per cent of normal and that it was controlled after the administration of vitamin K emphasizes the concept of the relation of pain to hemorrhage within the wall of the coronary artery. Pain recurred when there was a return of hypoprothrombinemia. It is suggested that if routine prothrombin determinations are carried out on all patients, the detection of an early hypoprothrombinemia and the prompt use of vitamin K should be factors in reducing the incidence of acute coronary occlusion.

(H. McG. Doles, *South Med Journ Birmingham, Ala* 1947, p. 905)

VITAMIN K IN THERAPY OF ESSENTIAL HYPERTENSION Morelli and Savli found that (1) the formation of cholinesterases is increased in the blood serum of patients with essential hypertension and that (2) the intravenous injection of a solution containing 10 mg of synthetic vitamin K (menadione, 2-methyl-1,4 naphthoquinone) diminishes both hypertension and the formation of cholinesterases in the blood serum of patients. The authors believe that essential hypertension is due to an imbalance of the autonomic nervous system with sympathetic predominance and that vitamin K stimulates the tonus of the autonomic nervous system and re-establishes its balance.

(A. Morelli and P. Savli, *Progresso Medico*, Oct. 1947, p. 611)

CHEMOTHERAPY OF URINARY INFECTIONS Hewitt stresses that necessary prerequisites for successful chemotherapy of infections of the urinary tract are a free flow of urine without obstruction, drainage of localized accumulation of exudate, absence of foreign bodies within the urinary tract or wounds tract, and renal function sufficient to secrete the chemotherapeutic agent in bactericidal concentrations in the urine. Mandelic acid has been largely supplanted by newer more potent drugs. Sulfathiazole and sulfadiazine are effective against almost all the common bacterial pathogens isolated from the urinary tract. The use of sulfonamide mixtures is a possible method for reduc-

tion of renal complications Penicillin is the most potent agent for the eradication of gram-positive cocci in the urinary tract, as well for the treatment of metastatic suppurative complications arising in the urinary tract during infections with these bacteria In the presence of mixed infection with gram-negative bacilli, combined treatment with sulfonamide compounds or streptomycin is effective against most of the gram-negative bacilli Resistent cultures of *Pseudomonas aeruginosa* and *Streptococcus faecalis* are an indication for increased dosage Alkalinization of the urine is an important adjunct to streptomycin therapy

(W L Hewitt, *Geriatrics*, Nov Dec 1947, P 334)

THERAPY OF BRONCHIAL ASTHMA Barach and Garthwaite point out that in patients who acquire refractoriness to epinephrine and aminophylline, temporary curtailment of the use of these bronchodilator drugs and substitution of other measures are required to obtain a remission from intractable asthma The effective administration of meperidine hydrochloride ("demerol hydrochloride" N N R.) in conjunction with continuous inhalation of 50 per cent oxygen is the simplest method to terminate a state of persistent bronchial spasm Intravenous injection of isotonic or hypertonic solutions of dextrose often is a helpful adjunct Physiologic therapy also includes helium-oxygen inhalations, positive pressure respiration, ether anesthesia, bronchoscopy and artificial fever therapy Antibiotic therapy for bronchial asthma by administration of penicillin, either intramuscularly or by aerosol, has value in selected cases The repeated introduction of penicillin aerosol into paranasal sinuses after the release of a previously established partial vacuum has been followed by clinical recovery in acute, subacute and chronic sinusitis and, in some instances, by clearance of the symptoms of intractable asthma The improvement after penicillin treatment or after physiologic therapy was sustained over two months in some patients, less than two months in others More sustained improvement after penicillin therapy appears to take place in patients in whom hyposensitization therapy with catarrhal vaccine and dust is instituted directly after treatment and continued for an indefinite period Current investigations of streptomycin and sulfadiazine and sulfathiazole aerosols point to the possibility that patients with mixed infection unresponsive to penicillin, therapy may be benefited by antibiotic treatment effective against both gram-positive and gram-negative bacteria

(A L Barach and Bettina Garthwaite: *Annals of Allergy*, 1947, p 297)

HYDANTION AS AN ANTICONVULSIVE DRUG Harris and Otto point out that since the advent of phenobarbital, diphenylhydantoin sodium ("dilantin" N N R) and trimethadione for control of grand mal and petit mal seizures, but, unfortunately, psychomotor attacks have responded poorly to these medications Their experience and that of other observers indicates that hydantoin, which is also known as "mesantion" (3-methyl-5,5-phenylethylhydantoin) is of great benefit in the treatment of psychomotor epilepsy and in cases of grand mal in which the illness has not been completely controlled by maximum tolerated doses of "dilantin" or phenobarbital, or in which, because of intolerance, the patients have not been able to take enough of the drugs to eliminate their attacks Psychomotor attacks, variously referred to as epileptic equivalent states, psychic seizures, psychomotor seizures, or

psychic equivalents, are often difficult to recognize and misinterpreted as behaviour disorders. Although the patient having such an attack usually has amnesia for the period, he may act as though he were conscious. The attacks ordinarily last only a few minutes but may go on for several hours or even days. During an attack the patient usually mumbles incoherently, performs some purposeless movement, such as buttoning and unbuttoning his garments, and frequently is incontinent. He is likely to be irritable, especially if an attempt is made to restrain him. The results of treatment of psychomotor seizures with "mesantoin" obtained by the authors was that 18 of 20 patients had been completely free of seizures for periods ranging from two to six months at the time of this report. Each of these patients was having an average of at least two seizures a month at the time "mesantoin" therapy was started. Six patients reported a reduction of 50 per cent or more in the frequency of attacks. One patient could see no improvement and discontinued treatment after one month. Five patients thought that they were unusually drowsy on "mesantoin" but none was handicapped to the extent that he wanted to discontinue treatment.

(T. H. Harris and J. L. Atto *Texas State Jour of Med* Sept 1947, p 328)

THIAMINE POTENTIATED WITH NEOSTIGMINE FOR HERPES ZOSTER Waldman and Perner say that most of the action of thiamine can be explained on the basis of its inhibition of cholinesterase, thus liberating more acetylcholine. This is precisely the mechanism of action claimed for neostigmine. As soon as the diagnosis of idiopathic herpes zoster was established, 1 cc of thiamine chloride (100 mg per cubic centimeter) and 1 cc of neostigmine methylsulfate (1:2,000) in the same syringe were given intramuscularly. The dosage was repeated every other day until the severe pain was relieved. The number of injections required to induce relief varied. The age of the patient and the duration of symptoms prior to treatment seem to play a part. The authors used the combined administration of thiamine and neostigmine in 28 cases of idiopathic herpes zoster. The results were sufficiently impressive to warrant further trial of this mode of treatment.

(S. Waldman and L. Perner *New York State Jour of Med* Sept. 1947 p 1007)

Original Contributions

PELLAGRA IN INDIA

by

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Raman (1940) reviewed the literature of pellagra in India and reported 25 cases. Since the publication of this paper, cases have been observed from different parts of India, Goodall (1940) 3 cases of pellagra and 12 cases of nicotinic acid deficiency from Calcutta, Carruthers (1941) 10 cases from Miraj, Bombay Presidency, Ahmed (1942) 6 cases of pellagra and some more cases of nicotinic acid deficiency from the United Provinces, Batra (1942) 20 cases from Bilaspur State in Simla Hills, Patel and Shah (1942) 10 cases from Bombay, Patel and Motashaw (1942) 15 cases from Bombay, Varma (1943) a typical case of pellagra with mental symptoms from Patna (Bihar), Napier and Chaudhury (1943) a case of recurrent pellagra in a myxoedematous patient from Calcutta, Dey (1943) cases from Bengal and Rao (1947) Mysore. In the Madras Presidency cases have been observed in Madras city and in the Andhra districts from Nellore, Guntur, Kurnool, Kistna, East and West Godavari, and Vizagapatam. The increased incidence is not due to the increase in the disease but is mainly due to the recognition of these cases and the medical officers becoming more pellagra conscious.

The present paper is a clinical study of 102 cases observed by the author, and includes the 37 cases already reported. In 1939 there were 10 cases, and in 1940, 16, but in 1942 only a single case was observed probably due to change in the conditions brought about by World War II. The incidence again gradually increased and in 1943, 6 cases were admitted into the King George Hospital.

Classification of pellagra—The classification suggested by the author (Raman, 1940) is adopted in this paper. 1. Primary pellagra (70 cases) showing symmetrical exfoliative dermatitis with a distinct line of demarcation, with or without the other symptoms of pellagra. 2. Primary pellagra with incidental disease (5 cases). The co-existent disease has practically nothing to do either with the onset or with the progress of the disease. 3. Secondary pellagra (27 cases). Pellagra developing in the course of other diseases. Here the co-existence disease has either precipitated the onset of pellagra or made the condition of the patient worse. The associated conditions in secondary pellagra were —

- 1 Beri beri and other clinical syndromes due to deficiency of the other components of Vitamin B complex such as Avitaminosis B₁, Ariboflavinosis and Oro-genital syndrome
- 2 Rickets
- 3 Diabetes mellitus
- 4 Gastrectomy for duodenal ulcer
- 5 Gastro jejunostomy for duodenal ulcer
- 6 Tuberculosis, miliarv, abdominal
- 7 Leprosy
- 8 Carcinoma (penis)
- 9 Congenital syphilis

Abstracts of a few interesting cases are given below —

Beri-beri and pellagra (case 1) — A A, male aged 30 years, was admitted on 18 9-43 with a history of tingling and numbness all over the body and inability to walk, of 3 days' duration. He was not married, and not addicted to alcohol. Physical examination showed a moderately nourished individual with oedema of the feet, red tongue, and symmetrical exfoliative dermatitis on dorsum of both the forearms. Heart showed enlargement both towards the right and left with a systolic murmur in the mitral area. Respiratory system was normal. The patient was constipated. Nervous system showed loss of deep reflexes and tenderness of the calf muscles. Urine showed a trace of albumin, but no casts. The patient was treated with injections of vitamin B₁ (10 mg a day) subcutaneously and nicotinic acid (100 mg) intramuscularly. Dermatitis and oedema of feet disappeared and the heart became normal in size, the size of the heart being controlled by radiograms. The patient was discharged cured on 28 10-43.

(Case 2) A second case of pellagra associated with beri beri was seen in a male aged 51. He was admitted on 11 2-40 with a history of dermatitis of 3 months' duration on the dorsum of the hands and forearms. He had an attack of beri beri 1½ years ago. Physical examination revealed an ill nourished individual with anaemia, oedema and exfoliative dermatitis on the dorsum of both hands, forearms and legs. There was ulceration of the lower extremities over the area of dermatitis with a few vesicles, as a result of application of petrol, a treatment suggested to him by his son who was a motor driver. Heart was enlarged and systolic murmur was present in the mitral area. Deep reflexes were lost. Urine was normal. His memory was poor, and in the hospital he developed marked mental symptoms such as melancholia, hallucinations and confusional insanity. A lumbar puncture was done and C S F showed increased protein (85 mg), chlorides 630 mg, sugar 47 mg per 100 c.c. and the presence of globulin. Colloidal Gold Reaction 0001222000. The patient gradually became worse and died on 16 2-40 of septic bronchio pneumonia as a result of infection from the infected leg. Post-mortem was done on 20 2-40 and showed in addition to the dermatitis characteristic of pellagra enlarged heart, intense congestion of all the organs, septic bronchitis of both lungs going on to bronchio pneumonia, congestion of the brain, and soft diffused spleen.

Pellagra and avitaminosis B₁ (case 3) — U P, male aged 30 years, was admitted on 6-5-39 with symptoms of advanced peripheral neuritis of 3 months' duration. Physical examination showed advanced peripheral neuritis without any oedema or cardio-vascular disturbance. Lumbar puncture showed proteins 8 mg, trace of globulin, chlorides 768 mg, and normal colloidal gold reaction, and normal cell count. Blood calcium was normal. Glucose tolerance test was within limits. Wassermann both of blood and cerebrospinal fluid was negative. Examination of the eyes showed concentric contraction of the field of vision and the patient rapidly improved with injections of vitamin B₁ and was discharged practically cured with wider fields of vision. This case was already reported (Raman, 1940).

He was readmitted on 15 2-40 (Fig 2) with symptoms of advanced pellagra. Physical examination the patient was semi-conscious, passing 8 to 10 motions per day containing mucus. There was general anasarca. Exfoliative dermatitis, typical of pellagra, was seen on the dorsum of hands and feet. Symptoms of peripheral neuritis were present. Examination of the fundus showed optic atrophy of both the eyes. Urine was normal. Motion showed mucus but was negative for ova and cysts. Blood showed microcytic anaemia. Laevulose tolerance test done on 16 2-40 showed a normal curve.

He was treated with liver extract and nicotinic acid and he gradually improved (Figs 3 & 4). He was discharged cured of the symptoms of pellagra on 21 8 40 but the symptoms of peripheral neuritis persisted.

During the years from 1940 to 1947 he used to present himself for examination once or twice a year with the same symptoms of peripheral neuritis but without any evidence of pellagra. Examination of the eyes showed optic atrophy and contraction of the field of vision.

Advanced pellagra with mental symptoms, recovery after massive doses of nicotinic acid and death by cellulitis and septicaemia (case 4)—U.S., male aged 36 years, was admitted on 27-3-38 for pellagra. He first came to the hospital for treatment of his nose, later he was referred to the Dermatologist for the condition of the skin, who finally transferred the case to me. He was a fairly nourished individual who had subjective symptoms of peripheral neuritis, but physical examination was negative. Pellagrous dermatitis was seen on the dorsum of hands and feet and in addition had an oval patch 1" by $\frac{1}{2}$ " with commencing exfoliation at the centre on either side of the neck. The patches on the lower extremities extended a little above the level of the knees and to the medial aspect of the thigh also. Circulatory and respiratory systems were normal. Blood count: R B C 5.03 million, W B C 5,600, Hb 75%, poly 75, mono 7.5, lymph 13.5, and eos 4%. Blood smear was normal. Fragility of the R B C was normal. Van den Bergh reaction negative both direct and indirect. Blood chemistry: total proteins 5.456, albumin 3.042, globulin 2.092, and fibrin 0.322 g per 100 c.c. Blood urea 34, sugar 91, calcium 9.9 and phosphates 2.8 mgs per 100 c.c. Gastric analysis, stomach was empty in 1½ hour, total acidity was low and free HCl was absent in all the specimens. Radiological examination after barium showed nothing abnormal. Section of the skin under microscope showed at the surface adherent keratinised scales, granular layer thin but visible, spinous layer thin and stretched out and papillae flattened out in several places. Melanin pigment was seen not only in the basal layer but in two or three layers above it also. Dermis was oedematous but showed no inflammatory reaction. Chromatophores showed increased deposit of melanin, and sweat and sebaceous glands were normal. The patient was given a liberal diet with eggs and liver soup, and liver extract (campaion) injections 2 c.c. every day. He improved considerably and was discharged on 12-4-38.

Six months later there was recurrence of the symptoms and injections of liver extract relieved the condition. Two months before the second admission the patient developed mental symptoms of depression and melancholia.

He was readmitted on 15-1-40. Physical examination showed that the patient was unconscious with bleeding gums, but there was no cyanosis or oedema. A few patches of dermatitis were present on the dorsum of hands and feet. Heart was normal. Pulse 86, blood pressure 110/65. Liver and spleen were just palpable below the costal margin. Respiratory system was normal. Nervous system: the patient could not be roused and though he could mutter a few words incoherently, could not answer questions. Pupils were dilated and equal. Deep reflexes were exaggerated, plantar response was flexor on both sides, and abdominal reflexes sluggish. Urine was normal. Blood: R B C 4.3 million, W B C 8,400, Hb 80%, poly 67, lymph 24, eos 3 and mono 6%. Fundus was normal. Blood urea 72, calcium 9.2, and cholesterol 154.7 mg per 100 c.c.

Lumbar puncture was done on 18-1-40 and the fluid showed sugar 52 and chlorides 690 mg per 100 c.c. Colloidal gold reaction was normal.

The patient was treated with increasing doses up to 300 mg of nicotinic acid intravenously and 100 mg by mouth, but his condition improved only slightly and the dosage had to be increased up to 1000 mg a day, 800 mg by injection and 200 mg by mouth. Then the amount of nicotinic acid was gradually reduced, and he had on the whole 18,050 mg. The patient rapidly recovered and walked out of the hospital completely cured of his physical as well as mental condition.

He reported again for examination which was negative on 13-3-40, was kept under observation and was discharged a week later. A year later the patient had an attack of diarrhoea in his village and was given subcutaneous saline. He developed cellulitis of the axilla and toxæmia and was admitted in the surgical ward for this condition. In spite of surgical interference the patient died of cellulitis and toxæmia a few days later.

Summary—A case of pellagra with dermatitis of the neck, hands and feet, improved rapidly by injections of liver extract, had a recurrence and was again cured by injections of liver extract. Mental symptoms developed which disappeared with massive doses of nicotinic acid, and the patient was discharged cured. He developed gastro-enteritis in his village, and cellulitis of the axilla after saline infusion and died of septic absorption and toxæmia.

The Indian Physician, June 1948

Pellagra and pulmonary tuberculosis (case 5)—A boy aged 12 years was admitted on 10 1-42 with symptoms of extreme weakness, emaciation, and low fever of 2 weeks duration. Physical examination showed general anasarca, angular stomatitis, superficial glossitis and symmetrical exfoliative dermatitis over the dorsum of the feet. Lungs showed tubercular infiltration of both sides, left more advanced than the right. He was running a fever between 100°F and 103°F while in the hospital. Urine was normal. Blood showed leucocytosis and sputum was full of tubercle bacilli. Sedimentation rate 28 mm. With the administration of nicotinic acid his pellagra disappeared and he was transferred to the Tuberculosis Department for his lung condition.

A male aged 40 years was admitted on 5 2 40 with symptoms of extreme weakness, emaciation and low fever. Physical examination showed a poorly nourished individual with oedema and symmetrical exfoliative dermatitis on the dorsum of both hands and feet. Symptoms of peripheral neuritis were present. Lungs showed advanced tuberculosis on both sides and sputum was positive for tubercle bacilli. He was treated with liver extract and nicotinic acid. Symptoms of pellagra disappeared but the tuberculous condition persisted. He was discharged relieved on 10-4-40.

A case of secondary pellagra associated with tuberculous ulceration of the caecum, showed slight improvement after treatment with liver extract and nicotinic acid, later the condition deteriorated, developed broncho pneumonia and died (case 6)—V P, male aged 40 years, a destitute, was admitted on 16 7 41 with a history of peripheral neuritis and cough of one year's duration. He was addicted to alcohol. Physical examination showed an ill nourished individual with extreme emaciation, anaemia, angular stomatitis and superficial glossitis but no jaundice, no cyanosis and no oedema in any part of the body. Liver and spleen were normal. A few lumps could be felt in the abdomen. Respiratory system did not show anything abnormal clinically. There was generalised wasting of all the muscles, deep reflexes were exaggerated, plantar response was flexor, and visceral reflexes were normal. Exfoliative dermatitis with well defined margins was present on the dorsum of hands and feet. Blood pressure was normal. Urine and motion showed no change.

The patient was started on injections of nicotinic acid 50 mg a day, with only slight improvement. Liver extract was given in addition, and the condition of the patient remained more or less the same. He lost 6 lbs after admission, his original weight being 68 lbs. The general condition of the patient steadily deteriorated in spite of injections of liver extract and nicotinic acid and the patient died on 30 11-41.

Postmortem examination on the same day showed general emaciation, dermatitis of the lower extremities, atrophy of the heart, congestion of the liver, broncho pneumonia, gastritis, and extreme tuberculous ulceration of the caecum with involvement of the lymphatic glands. Small areas of haemorrhage and softening were observed in both the hemispheres of the brain.

Summary—A case of secondary pellagra associated with tuberculous ulceration of the caecum. The patient was in a low condition at the time of admission showed dermatitis of the dorsum of hands and feet. Improved to a certain extent by injections of nicotinic acid and liver extract. The condition gradually became worse and the patient died of broncho-pneumonia. Postmortem showed tuberculous ulceration of the caecum, broncho pneumonia and cortical haemorrhages.

Pellagra with advanced peripheral neuritis and lesion of the optic nerve (case 7)—P P, male aged 40 years, was admitted on 23 11-45 with a history of peripheral neuritis of 6 years' duration. His vision was dim for the last one year. Pellagrous dermatitis was present on the dorsum of hands and feet. Peripheral neuritis was present. Eyes vision in both eyes, fingers at 5½ meters' distance, fundus examination showed pallor of both the optic discs and concentric contraction of field of vision of both the eyes. He was treated with injections of nicotinic acid and vitamin B₁ and was discharged cured on 25 12-45.

An advanced state of pellagra in an individual with essential hypertension admitted in an unconscious condition. Treatment with nicotinic acid improved the condition and the patient was discharged relieved (case 8)—K T, male aged 50 years, was admitted in an unconscious condition on 31 1-46. Physical examination at the time of admission (8 a.m.) showed dilated pupils, not reacting to light, slight rigidity of the neck alternating with flaccidity and low muttering delirium. There were no signs or symptoms of localisation of cerebral lesion. Knee jerks were normal, and

plantar response was flexor on the right and indefinite on the left. Heart was hypertrophied, systolic murmur was heard in the mitral area and the 2nd sound in the aortic area was accentuated. Blood pressure was 175/105. Lungs showed moist sounds at both the bases. Spleen and liver were normal. Symmetrical exfoliative dermatitis was present on the dorsum of hands and feet.

Blood smear did not show any malarial parasite. Urine showed a trace of sugar, but no albumin. Lumbar puncture showed cerebro spinal fluid under normal pressure, proteins 30 mg and presence of globulin. There were 3 cells per c mm. Blood urea on 31-1-46, 61 mg, and sugar 106 mg per 100 c c. The question arose whether the condition was one of hypertensive encephalopathy, or one of pellagra only. He was given injections of nicotinic acid 200 mg, intravenously morning and evening. The next day the patient's condition became better and he was able to talk. On questioning, he was able to give history of diarrhoea of 3 years' duration. The patient gradually improved but the blood pressure while in the hospital varied between 170 to 208 systolic and 105 to 110 diastolic. The patient gradually became better, the pellagrous dermatitis disappeared and nicotinic acid was continued till the day of discharge.

Summary—An old man was admitted unconscious, physical examination showed hypertension and pellagrous dermatitis. The question arose whether the condition was a cerebral lesion such as hypertensive encephalopathy or the whole condition was pellagra only. Treatment with nicotinic acid in large doses relieved the patient's condition and he was discharged relieved.

Recurring pellagra of 3 years duration associated with deficiency of total acidity and absence of free hydrochloric acid, admitted with mental symptoms and discharged relieved (case 9)—B. A., male aged 35 years, was admitted on 16-2-39 with a history of chronic dyspepsia of 8 years' duration. He was addicted to alcohol. The condition used to recur every year and this was the 3rd attack. Physical examination showed a moderately nourished individual with anaemia and exfoliative dermatitis of the dorsum of hands and feet. Nervous system—intelligence slightly low, deep reflexes lost, sensations normal, subjective sensations of tingling and numbness present. Heart and lungs normal. Blood pressure 95/75. Urine normal. Blood showed normocytic anaemia. Motions no ova, no protozoa. Gastric analysis—

| 4-3-39 | Total acidity | Free HCl | 31-5-39 | Total acidity | Free HCl |
|--|---------------|----------|---------------------------------------|---------------|----------|
| Resting juice 32 c c alkaline, contains bile | | | Resting juice 80 c c Total acidity 32 | | |
| | | | Free HCl nil | | |
| 1 hr | 1 | nil | | 1 | nil |
| 1 hr | 1 | nil | | 4 | nil |
| 1 hr | 1 | nil | | 4 | nil |
| 1 hr | 2 | nil | | 4 | nil |
| 1 hr | Alkaline | | | 6 | nil |
| 1 hr | 1 | nil | | 8 | nil |
| 1 hr | 1 | nil | | 5 | nil |

Bile present in all the specimens

Bile absent in all the specimens

Blood urea 33, and sugar 105 mg per 100 c c. Blood proteins total 3.609, albumin 2.123, globulin 1.338, fibrin 0.208 g. Van den Bergh reaction—direct positive delayed, indirect positive. Quantity insufficient for estimation.

The patient rapidly improved with nicotinic acid 90 mg, and acid hydrochloric dil 3 dr a day by mouth, and was discharged relieved on 9-4-39. He was readmitted the next day with symptoms of mental deficiency, and was again put on nicotinic acid by mouth. When these tablets were given to him he used to hide them under his pillow, and so they had to be put into his mouth. This he used to spit out and consequently it had to be given intravenously. The patient had a course of injections of nicotinic acid for about a week. A second gastric analysis done on 31-5-39 showed slight increase in total acidity but free HCl was still absent. The patient was discharged relieved on 26-8-39.

Summary—A case of recurrent pellagra with mental symptoms and deficiency of total acidity with absence of free HCl in the stomach. He was discharged relieved and readmitted next day with symptoms of definite mental deficiency. Increasing doses of nicotinic acid intravenously and HCl by mouth improved the patient's condition. A second gastric analysis showed the total acidity was increased but free HCl was still absent.

Secondary pellagra associated with leprosy (case 10)—M. K., male aged 50 years was admitted on 21-3-45 with a history of exfoliative dermatitis of 15 days' duration.

Physical examination showed pellagrous dermatitis on the dorsum of hands and feet. There was no oedema in any part of the body. The patient had leprosy. His ulnar and external popliteal nerves were thickened and he had a perforating ulcer on the right foot. Circulatory and respiratory systems were normal. Deep reflexes were absent, anaesthetic patches of leprosy were present on the right leg. The patient was treated with nicotinic acid, the pellagrous dermatitis disappeared and he was transferred to the Dermatological Department for the treatment of leprosy.

PELLAGRA IN INFANTS AND CHILDREN

(1) *Primary pellagra (case 11)* — A girl aged 5 years was admitted in November 1944 with symptoms of pellagra of 2 weeks' duration. Physical examination showed a poorly nourished individual with anaemia, angular stomatitis, superficial glossitis and areas of dermatitis, (i) right round the neck, (ii) on the dorsum of the hands and at the elbows, both in front and behind, (iii) on the gluteal and the inguinal regions, (iv) right round the knee both in front and behind and (v) right round the ankle (Figs 21 & 22). The child rapidly improved with nicotinic acid and the dermatitis disappeared but had to be discharged before complete cure as the relations insisted on taking the child away.

(2) *Primary pellagra (case 12)* — A girl aged 8 years was admitted in 1944 with symptoms of indigestion and loss of appetite. Physical examination showed exfoliative dermatitis of pellagra on hands and feet. The child was treated with nicotinic acid and was discharged cured.

(3) *Congenital syphilis and pellagra (case 13)* — G.P., a child aged 9 months was brought to the out-patient department on 13.2.41. The child was the 5th in rank and the only one alive, all the previous children having died of congenital syphilis. The child was partly breast fed and partly on cow's milk and other artificial food. Physical examination showed a poorly nourished child with oedema of the hands and feet with stigmata of congenital syphilis and in addition symmetrical exfoliative dermatitis with well defined margins over the hands and feet (Figs 18 and 19). Patches were also present on the face. The condition of the child was very bad no further investigation could be done as the child died within 2 hours after admission.

(4) *Rickets and pellagra (case 14)* — A girl aged 18 months was admitted in July 1945 with signs of rickets. The child was put on cod-liver oil and she gradually improved. But two weeks later, while in the hospital with a liberal diet and cod liver oil, the child developed symmetrical exfoliative dermatitis with well defined margins on the dorsum of both the forearms (Fig. 20) more marked on the right than on the left. The child was put on nicotinic acid by mouth, 50mg per day when the dermatitis completely disappeared, and was discharged. Three weeks later, the child was again admitted for symptoms of rickets. But this time there was no evidence of pellagra. The child died in an attack of convulsions (spasmophilia).

SYMPTOMATOLOGY

All types of cases from the mildest to the most advanced and severe forms resulting in death are found in the series. In some cases, the patients were quite unaware of the condition, came to the hospital for some other complaint and the diagnosis was made only by routine examination.

(1) *Dermatitis* — The presence of the skin lesion is definitely diagnostic of pellagra, but in cases where the skin lesion has disappeared, diagnosis becomes difficult and there were cases in this series with only a history of dermatitis a few months before admission. The dermatitis as met with in Indians usually starts as a red hyperaemic area simulating burn of the first degree. On the 3rd day it becomes dark red in colour, in another 2 days it changes to light brown, then to dark brown and finally becomes black in colour. The whole process usually takes about 2 to 3 weeks. The margins become well defined, exfoliation begins at the centre, and the area left after exfoliation is paler than normal. The extension of the patch usually occurs at the periphery and when a definite line of demarcation is formed, no further extension occurs.

They are usually met with on the dorsum of hands and feet, in some cases it might extend up above the elbows or might come down even to the proximal phalanges. It was never observed in the terminal phalanges. In the lower extremity the patch might extend up to the thighs. Patches were also observed on the face and on the neck in 6 cases (Casal's necklace). Extensive areas of dermatitis were also observed practically extending over half the body and even in these cases a definite line of demarcation could be made out between the normal and the pellagious skin. The unusual situations were under the breasts in women, on the groins and thighs and lastly on the popliteal fossae. In children the usual distribution of dermatitis was not seen, and they might be present either on the flexor or extensor aspects (Figs 21 & 22). Unilateral lesions were observed in two cases (Fig 14). Bean et al (1944) found unilateral or asymmetric cutaneous lesions in 32 (3.4%) of 889 cases and suggested that localised trauma might be responsible for this type of lesion.

Histo-pathology of the skin has been described in detail previously (Raman, 1940) and consisted in changes both in the epidermis and in dermis. In the epidermis, the horny layer showed hyperkeratosis, stratum granulosum was thin, stratum spinosum first showed proliferative activity and in chronic stages became thin and papillae disappeared. In the dermis there was increased activity of chromatophores and the papillae disappeared. Occasionally oedema and polymorpho-nuclear infiltration were found in some cases in relation with smaller capillaries and lymphatics. These areas of cellular infiltration cannot be taken as evidence of inflammatory granulomatous condition of the skin. Hair follicles atrophy, sebaceous and sweat glands are usually normal but may be atrophied in advanced cases. Moore et al (1942) studied the histopathology of the skin in 15 cases and found that skin, from both the affected and unaffected areas showed hyperkeratosis but parakeratosis and acanthosis were found only in the affected areas.

(2) *Gastro-intestinal symptoms*—Loss of appetite was the symptom complained of by many. Diarrhoea also occurred but it was a common feature in the terminal stage of the disease. But several patients have come to the hospital in the earlier stages with absolute constipation for 3 or 4 days. Angular stomatitis and superficial glossitis were often met with but may be absent in some cases. In cases of secondary pellagra associated with tubercular enteritis, masses may be felt in the abdomen.

Gastric analysis was done in 17 cases. Case No 9 showed diminished total acidity and absence of free HCl. As a result of treatment though the total acidity increased, free HCl continued to be absent. Usually the total acidity was low and as the condition advanced the total acidity was diminished still further and free HCl completely disappeared. Histamine was not given in these cases to test the histamine fast acholrhydria. One case definitely showed a curve of duodenal ulcer and this patient was operated for duodenal ulcer showing that pellagra can occur or develop in individuals with increased acidity.

(3) *Nervous system*—Patients usually complained of tingling and numbness but on physical examination nothing abnormal could be made out. There were cases in which definite signs of either peripheral neuritis or of subacute combined degeneration were present, (i.e.

exaggeration of reflexes and presence of Babinski's sign) When cases were associated with beri-beri or avitaminosis B₁, the peripheral neuritis was a marked feature. Mental symptoms such as loss of memory, incoherent speech, depression, melancholia and acute mania were observed in a few cases. In some of these, they occurred before, in some during and in the others after the attack of pellagra.

The condition of the optic nerves was investigated in 16 cases (11 of these have already been reported, Raman and Abu, 1941) and 8 cases showed varying changes consisting of pallor of the temporal side of the optic disc, contraction of the field of vision in the temporal half, concentric contraction of the field of vision and optic atrophy. Gonzalez (1942) reported optic neuritis in 7 patients, 3 of whom were alcoholic addicts.

Cerebro-spinal fluid—Twelve cases were investigated and pressure of the fluid was normal in all. Five cases showed low proteins varying between 5 to 8 mg per 100 c.c., two cases showed definite increase, one 30 and the other 95 mg. Globulin was present in two cases. Chlorides were normal except in three cases that showed low values and the lowest was 600 mg. Cells were normal in all. Colloidal gold reaction was done in 8 cases and was abnormal only in one case that showed a meningitic curve. Blood sugar was normal except in one case in which it was low (47 mg). Wassermann reaction was done in 7 cases, it was doubtful only in one, and was negative in all the others. Pellagra in itself does not produce any changes in the cerebro-spinal fluid. The one case that showed definite changes (case 2) consisting of increased proteins with the presence of globulin, low chlorides, low sugar and meningitic curve in colloidal gold reaction had septic broncho pneumonia, and post-mortem showed congestion of the brain.

(4) *Circulatory system*—Primary pellagra did not show any changes in the heart but when associated with beri-beri, cardiac changes of beri-beri were present. Usually the blood pressure was normal. In a patient associated with pulmonary tuberculosis the blood pressure was 90/25, in another case associated with hypertension and mental symptoms (case 8), it was 176/115, and in a third patient who was admitted in an unconscious condition, the blood pressure was 175/105. In the last case, hypertension was a separate condition, blood pressure varied between 170 to 208 systolic and 105 to 110 diastolic, and when the patient was discharged free from mental symptoms the blood pressure was 180/110. In another case of primary pellagra which was previously reported (Raman, 1940) the blood pressure was 182/112.

Porter and Higginbotham (1941) from a study of the heart in 25 cases of pellagra found that there were no characteristic changes in pellagra either clinically, electrocardiographically or by post-mortem. The changes observed in some cases were due to other complications such as vascular disease, diabetes or alcoholism. A follow up of another 23 cases of pellagra showed neither congestive heart failure nor any other cardio-vascular lesion.

(5) *Respiratory system*—Four cases were associated with pulmonary tuberculosis and they were confirmed radiologically and/or by the presence of tubercle bacilli in the sputum. In all the other cases, the respiratory system was normal.



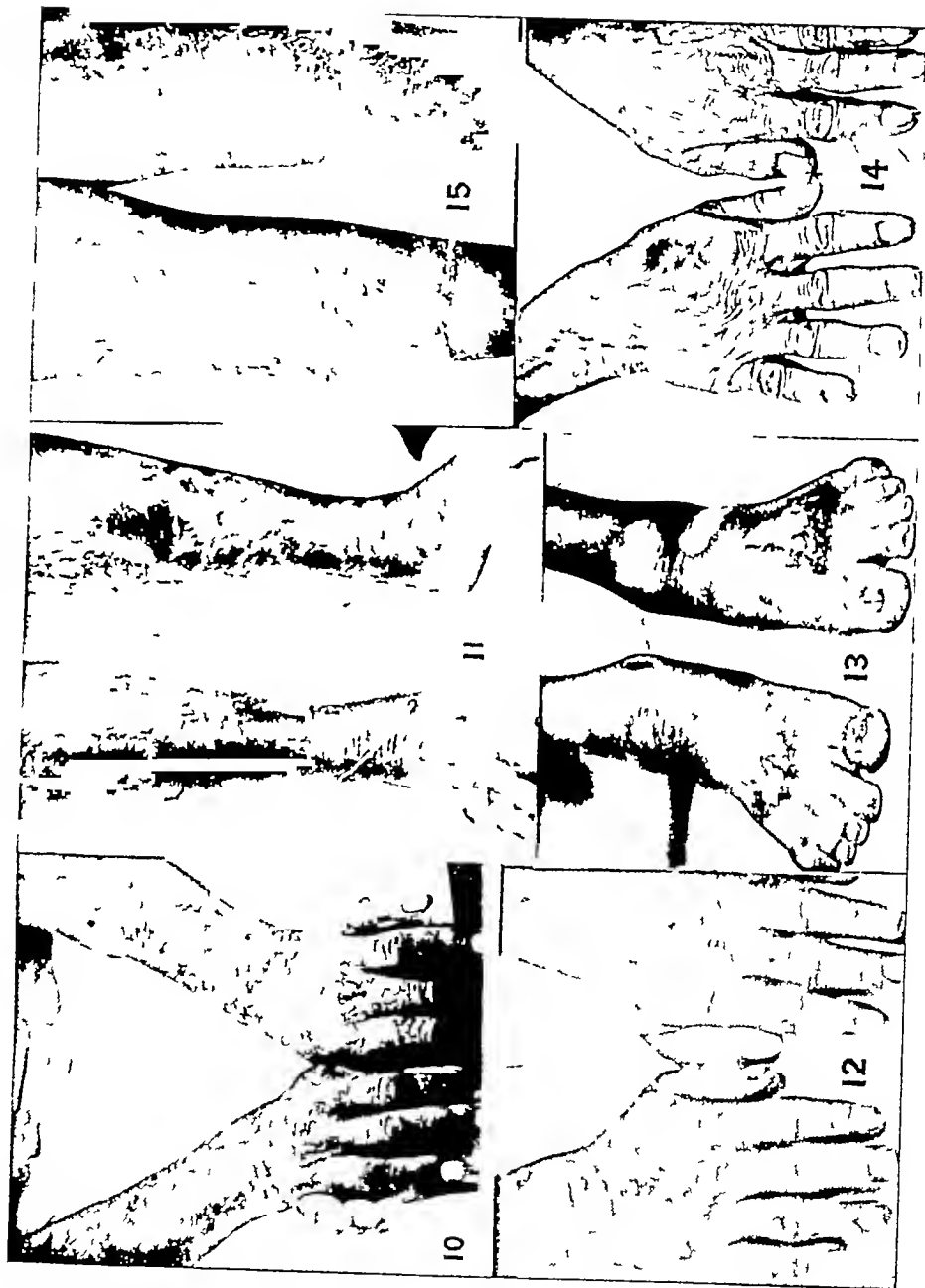
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RAMAN—PELLAGRA



RAMAN-PELLAGRA

PLATE 4

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(6) *Oedema* was present in 40 cases. Of these, 8 cases were associated with beri-beri. In all the others, oedema was due to diminution of plasma proteins.

Blood proteins were investigated in 28 cases and in 8 of them the blood was examined before and after the treatment. Different types of albumin globulin ratios were obtained and the findings are given in Table I.

TABLE I

| | | Total Proteins | Albumin | Globulin | Fibrin | |
|-----|---|-------------------|---------|----------|--------|---|
| | | % | % | % | % | |
| I | <i>Primary Pellagra</i> | | | | | |
| | (a) Before treatment | 5.003 | 2.166 | 2.802 | 0.335 | Total proteins low, and the proteins increased after treatment but the albumin globulin ratio was not much altered |
| | After treatment | 6.010 | 3.163 | 3.101 | 0.355 | |
| | (b) Before treatment | 7.364 | 1.417 | 1.524 | 0.223 | do |
| | After treatment | 5.520 | 2.272 | 2.858 | 0.890 | |
| II | <i>Primary Pellagra with incidental disease (duodenal ulcer)</i> | | | | | |
| | Before treatment | 7.015 | 3.255 | 3.520 | 0.270 | Total proteins normal at the beginning albumin globulin ratio altered. After treatment, the total proteins came down but the albumin globulin ratio became normal |
| | After treatment | 5.685 | 3.085 | 1.825 | 0.375 | |
| | (a) <i>with diabetes mellitus</i> | | | | | Total proteins normal, reversal of the albumin globulin ratio |
| | Before treatment | 6.257 | 2.708 | 3.208 | 0.341 | |
| III | <i>Secondary Pellagra</i> | | | | | |
| | (a) <i>with diabetes mellitus</i> | | | | | Total proteins low and reversal of albumin globulin ratio |
| | Before treatment | 5.513 | 1.666 | 3.511 | 0.386 | |
| | (b) <i>with pulmonary tuberculosis and tubercular peritonitis</i> | | | | | Total proteins low, but after treatment the proteins diminished |
| | Before treatment | 4.833 | 2.020 | 1.660 | 0.247 | |
| | After treatment | 3.030 | 2.434 | 1.300 | 0.205 | |

The total proteins were usually diminished, diminution mainly affecting the albumin fraction, and in some cases there was an increase in the globulin. The blood protein came to normal after treatment, but in some cases that did not respond to treatment, the proteins either remained the same or became diminished.

Blood picture Blood smears were examined in 85 cases, but blood counts and estimations of haemoglobin were done only in 40 cases. All types of anaemias were present, microcytic in 20, normocytic in 7, and macrocytic in 8 cases. Normal blood picture was present in 5. Blood picture improved after treatment with liver extract and nicotinic acid. Two cases of primary pellagra showed the following blood picture (Table 2).

TABLE 2

| | Blood count | | | Differential count | | | Haemoglobin | Halometer |
|---|----------------------|--------|-----------|--------------------|-----------|----------|-------------|-----------|
| | R.B.C. (millions) | W.B.C. | Poly % | Lymph % | Mono % | Eos % | | reading |
| 1 | 1 1 | | 70 | 23 | 3 | 2 | 30 | 4 03 |
| | 1 4 | | 73 | 18 | 3 | 6 | 30 | 5 00 |
| | 4 8 | 9,000 | 63 | 15 | 10 | 12 | 75 | 4 90 |
| 2 | 3 2 | 8,200 | 71 | 12 | 3 | 14 | 60 | 5 00 |
| | 3 4 | 9,283 | 57 | 19 | 4 | 20 | 75 | |

Macrocytic anaemia later on became microcytic and normal blood picture was restored after treatment. Microcytic anaemia occurred in the majority of cases. In cases that showed a leucocytosis with relative increase of eosinophils, the eosinophils decreased and in some cases when larger doses of liver extract were given, the eosinophils increased with fall of polymorphonuclear cells.

Van den Bergh reaction showed haemolytic jaundice in 25 cases, and in all these the quantity was too small for estimation.

Sedimentation rate was estimated in 6 cases. It was increased in 4 cases of secondary pellagra of which 2 were associated with tuberculosis, one with leucoderma, and one with peripheral neuritis and diarrhoea. Weekly estimations showed that the increased sedimentation rate persisted even after cure of the pellagrous condition but in one case associated with diarrhoea and peripheral neuritis, the sedimentation rate became normal after 8 weeks. It was normal in the other two cases.

Pellagra produces no change in the sedimentation rate. The change if any is produced by the associated condition and when that disappears the change in sedimentation rate also corrects.

Sugar, urea, calcium and phosphorus in blood have all been estimated and the findings were the same as those reported before (Raman, 1940).

Levulose tolerance test was done in 9 cases and the findings are discussed elsewhere.

Fat analysis of the stools was done in 8 cases and the findings of two cases are given below —

| | | Before treatment g% | After treatment g% |
|---|----------------------|---------------------------|--------------------------|
| (1) Primary pellagra | Total fats | 34.20 | 11.40 |
| | Unsoaped fat | 28.80 | 3.00 |
| | Free fatty acids | 9.09 | 2.37 |
| | Neutral fats | 18.81 | 0.63 |
| | Combined fatty acids | 24.21 | 0.03 |
| (2) Secondary pellagra associated with tuberculosis | Total fats | 42.60 | |
| | Unsoaped fat | 16.40 | |
| | Free fatty acids | 11.65 | |
| | Neutral fats | 4.75 | |
| | Combined fatty acids | 30.05 | |

The first case showed increase in the total fats with relative increase both in the neutral fats and free and combined fatty acids showing that there was both defective digestion and defective absorption of fats. The fat content became normal after treatment. In the second case there was considerable increase in the total fats but the increase was more marked in the combined fatty acids showing defective absorption. One more case showed increase in the split and unsplit fat. There was defect both in digestion and absorption.

RADIOLOGICAL APPEARANCE

Twelve cases were investigated with X-ray after barium and only in one case it was done before and after treatment. In this case the stomach was atonic (Fig 16) not emptying in 5 hours and a long retrocaecal appendix was visible in the 24 hours picture. A second picture (Fig 17) taken after treatment showed increased tone of the stomach wall. Two cases showed spasm of the pylorus, one case slight irregularity of the duodenal cap (gastric analysis showing low acidity with absence of free HCl), one case definite duodenal ulcer confirming the biochemical findings, one case evidence of duodenal ulcer (with normal gastric analysis), one case pyloric stenosis, and one case a normally functioning stomach after gastro-enterostomy. The other cases showed nothing abnormal.

Beams et al (1941) found increased motility of the gastro-intestinal tract in one case and in two cases the small intestine showed disturbance of the mucosal pattern with variations in size and contour of the lumen.

Rubio and Rolden (1942) studied the radiological appearances of 255 cases of pellagra in the course of 3 years and found that the tone of the stomach was decreased in 66.3%, and that there was dilatation and considerable delay in emptying in 68.1% of the cases. Repeated examinations in 59 cases during the different stages of the disease showed some relationship between the clinical aspect and the atonic condition of the stomach.

Fischer (1942) examined radiologically the condition of oesophagus in 17 cases of pellagra, who complained of difficulty in swallowing, and found constriction in those places where ulcerations were observed by oesophagoscopy. The condition was relieved by nicotinic acid, riboflavin and vitamin B₁.

DIAGNOSIS

The classical signs of pellagra usually described in text-books as dermatitis, diarrhoea and dementia are not usually observed in the early cases as they are manifestations of advanced cases or of late stages of the disease. Symmetrical exfoliative dermatitis is the main diagnostic feature of the disease, and in some cases this might be the only clinical manifestation though the other two may appear later.

(1) *Dermatitis* is exfoliative in character, usually symmetrical, with well defined margins generally occurring on the exposed parts of the body, though it may develop in unexposed parts also such as the axilla, groin, and under the breasts in women. In children, the dermatitis is not so characteristic as in adults. The definite line of demarcation is always present in the early stages, but later on it may disappear and with the advent of oedema the characteristic feature of pellagrous dermatitis is completely obscured. Vesicles and bullae have been described, but this was present only in two of my cases and these were associated with secondary infection.

(2) *Gastro-intestinal symptoms* such as angular stomatitis, superficial glossitis and diarrhoea are commonly met with, but in the earlier stages there might be constipation instead of diarrhoea. Diarrhoea is a constant feature in the terminal stages of the disease. Occasionally, the gastro-intestinal symptoms are entirely absent.

(3) *Nervous manifestations* Peripheral neuritis occurring in cases of pellagra is due to the associated deficiency of vitamin B₁.

Symptoms of subacute combined degeneration occurring in some cases may be due to the anaemia, usually macrocytic though microcytic anaemia also may show exaggeration of reflexes and extensor plantar response (Babinski's sign). Mental symptoms may occur, they may precede, accompany or follow the attack of dermatitis. Sometimes delirium and violent mania may develop.

Symmetrical exfoliative dermatitis with well defined margins occurring on the dorsum of both hands and feet is the main diagnostic feature of pellagra. Others are only accessory signs and without dermatitis the diagnosis of pellagra is not justified. The author makes a diagnosis of early cases of pellagra only when the dermatitis is present, or when the patient gives a history of dermatitis. Diagnosis of pellagra has been made in cases showing angular stomatitis, superficial glossitis and slight diarrhoea with or without mental symptoms and they rapidly responded to treatment with nicotinic acid. If there is a history of dermatitis in the patient the diagnosis of pellagra is definite.

DIFFERENTIAL DIAGNOSIS

(1) *Ichthyosis* In this condition exfoliation of the skin is present all over the body and there is no line of demarcation. This is a life-long congenital condition which runs in families, becoming worse during cold weather, nicotinic acid has no influence but thyroid may help.

(2) *Exfoliation of the skin occurring in cold season of the year (November to February)* In this condition the scales are fine and there is neither change of colour nor a definite line of demarcation as in pellagra. Exfoliation may occur also in the palms.

(3) *Oro-genital syndrome* (Nair, 1939) is diagnosed by angular stomatitis, superficial glossitis and a slight exfoliative dermatitis of the genitalia. There is no exfoliative dermatitis of the hands and feet or anywhere else in the body. The condition usually responds with nicotinic acid and riboflavine. Pellagra and oro-genital syndrome may coexist.

(4) *Sprue and sprue syndrome* The diarrhoea and the anaemia may simulate pellagra, but dermatitis is absent in this condition. But difficulty may arise in cases of pellagra after the dermatitis has disappeared.

(5) *Psychological condition* Mental condition of the patient such as delirium, mania or depression may stimulate mental diseases. But the presence or the history of dermatitis will distinguish the condition.

(6) *Ringworm* especially associated with dark pigmentation, occurring in the neck may be mistaken for pellagra. In this condition the margins are raised, and studded with fine papules and vesicles, the scales are fine and the fungus can be isolated. Both ringworm and pellagra may coexist in the same person and in same area of skin and even in this the diagnosis can be made out by demonstrating the causative fungus.

(7) *Dermatitis of unknown causation* A male aged 60 years was admitted on 1-10-38 for symmetrical exfoliative dermatitis over the dorsum of both hands and feet, and over the knees. The dermatitis had extended even to the terminal phalanges. Diagnosis of pellagra was

doubtful in this case. Section of the skin under microscope showed cellular infiltration with giant cell systems showing that the condition was either tubercular or leprosy in origin. Acid fast organisms could not be made out either in smears or in sections of the skin. Clinically the condition was not in favour of either tubercle or leprosy.

(8) *Kwashiorkor, Williams' disease, infantile oedema, Gullan's oedema, pellagroid beri-beri* (Trowell, 1941). Pellagra in infants and children has been described under these headings. Some of these descriptions fit in with infantile pellagra but some are modifications and probably associated with other vitamin deficiencies such as B₁, nicotinic acid or riboflavin. Similar cases are observed in Vizagapatam. Symmetrical exfoliative dermatitis with well defined margins is not present in these conditions.

TREATMENT

(1) *Diet*—The most important of all factors in the treatment of pellagra is the diet. Rice is the main article of diet in Vizagapatam. In the hospital the patients are usually given two kinds of diets, (i) the ordinary Indian diet, or (ii) milk and bread diet.

| (i) Ordinary Indian diet (hospital) | |
|-------------------------------------|----------|
| Rice | 1 lb.* |
| Bread | 4 oz. |
| Butter | 1 oz. |
| or Ghee | ½ oz. |
| Coffee (milk 3 oz. sugar 1 oz.) | 2 pints. |
| Buttermilk | ½ pint |
| Gingelly oil | ½ oz. |
| Plantain | 1 |
| Sugar | 1 oz. |
| Mutton | 4 oz. |
| Potatoes or vegetables | 4 oz. |

Mutton 4 oz. may be substituted by dhal 4 oz., or fish 4 oz. or eggs 2.

* The quantity of rice has now been reduced to 12 oz., fish or mutton to 3 oz., dhal to 2 oz. and potatoes or vegetables to 3 oz.

| (ii) Milk and bread diet (hospital) | |
|-------------------------------------|-----------|
| Milk | 1½ pints. |
| Bread | 12 oz. |
| Butter | 1 oz. |
| Sugar | 2 oz. |
| Coffee | 1 pint |
| Plantain | 2 |

In addition to this, the patient gets 2 eggs, and 8 oz. of liver soup daily. Patients who were treated as out patients were taking their usual diet in their houses.

| (iii) Ordinary diet taken by patients (at home) | |
|---|----------------------------------|
| Rice (milled) | 16 oz. to 20 oz.* |
| Ragi | 4 oz. every day or alternate day |
| Dhal | 2 oz. a week |
| Vegetables: brinjals, cucumber green leaves | 2 oz. once a week. |
| Buttermilk | 6 oz. occasionally |
| Fish or mutton | 4 oz. once a week. |

* The quantity of rice is now reduced (10 to 12 oz.) and is not milled.

(2) *Liver*—Liver was given either by mouth or by injection. For oral administration, the liver may be cooked or fried, but over cooking has to be avoided. It may be given in the form of curry or soup. Injections of crude liver extract were given in all the cases depending upon the seriousness of the condition of the patient. In one case the patient had 4 c.c. per day, later it was reduced to 2 c.c., then every alternate day, then twice a week and finally once a week. This minimum dose was continued for at least 2 months. Refined liver extracts did not show any marked improvement but when changed to one of crude liver extracts, the response was very good. As pointed out before, injections of liver extract sometimes produced eosinophilia and in cases that show-

ed eosinophilia before treatment, the count came down to the normal level after treatment

(3) *Iron*—If the anaemia is microcytic, ferri et ammonium citras 60 to 90 grains per day or Bland's pill 15 grains 3 times a day was usually given

(4) *Hydrochloric acid*—Acid hydrochloric dil 20 min to 1 dr 3 times a day was given in all the cases especially those showing deficiency of HCl. A second gastric analysis done in two cases did not show any change in the acidity

(5) *Nicotinic acid* (Niacin)—In the author's previous communication (Raman, 1940) the dosage of the nicotinic acid used was small. Later, larger doses were given, 100 to 150 mg per day. This was usually given for a fortnight and the dermatitis rapidly disappeared. This also produced marked improvement in the general condition of the patient. In serious cases, nicotinic acid had to be given parenterally, usually intramuscularly. It was recommended that for intra-muscular injections the nicotinic acid must be diluted, but by an accident, an injection was given without any dilution and no toxic symptoms occurred. Afterwards for intra-muscular injections nicotinic acid was always given undiluted but intra-venously, it was given always diluted either with saline or glucose. In case (No 4) the patient had 800 mg by injection per day every 4 hours and thus produced a rapid improvement in the patient's mental condition.

Toxic reactions of nicotinic acid were very few during the earlier days but later, flushing of the face was a constant symptom especially when given intravenously. Even greater dilutions made no change and this reaction usually appeared within 5 minutes after injection and disappeared in another 15 minutes. No accidents have so far been observed after nicotinic acid therapy.

Associated deficiency of vitamins such as B₁ and riboflavine were treated with vitamin B₁ or riboflavine or vitamin B complex which contains both.

(6) *Folic acid*—In cases associated with macrocytic anaemia, folic acid 5 to 80 mg a day by mouth may be given. Spies (1946) found considerable improvement in 46 cases of pellagra showing macrocytic anaemia.

(7) *External medication*—Ointments and lotions have been recommended for dermatitis but none of these had any effect except as palliatives and emollients. When secondary infection occurs, it has to be treated like an infected ulcer.

Deaths

Harris (1941) from a study of the cases observed in the U.S.A. in 1938 recorded deaths varying from 0.1 to 1.8 per 100,000 population, while Ruffin and Smith (1941) had 7% deaths in a series of 244 patients, six of whom died of pneumonia or peritonitis.

In the present series, there were ten deaths (9.8%) though post-mortem was available only in 6 of these cases. The first one was a case of secondary pellagra associated with pericarditis in a woman aged 85 years. She gradually became weaker and died. Post-mortem showed pericarditis, fatty nutmeg liver, infarction of the spleen and kidneys and

atrophy of the mucous membrane of the large intestine. The second case occurred in a male aged 35, a case of secondary pellagra associated with cirrhosis of the liver and septic meningitis. He was first treated with a liberal diet, liver extract injections and iron and hydrochloric acid by mouth. He steadily improved and was discharged cured. Three months later, he was readmitted with symptoms of cirrhosis of the liver. In the hospital the patient developed temperature varying between 100° to 103°F, became gradually worse and died. Post-mortem showed atrophic cirrhosis of the liver, slight hypertrophy of the heart, atheroma of the aorta, congestion of the lungs, enlarged spleen with perisplenitis and suppurative meningitis. The third case was a male aged 35 years who had an abdominal operation 4 years ago. Clinically, the condition looked like carcinoma of the stomach with pyloric obstruction, confirmed by gastric analysis and radiological examination. After his recovery from the pellagra he was transferred to the surgical department where an exploratory laparotomy was done. The whole of the peritoneum was studded with colloid tubercles, the liver was cirrhotic and biopsy of the nodule showed hyperplastic tuberculosis. The patient died a few days later and post-mortem showed diffuse tuberculous peritonitis, tuberculous ulceration of the small intestine, chronic ulcer of the stomach with pyloric stenosis, tuberculous lymphadenitis, subphrenic abscess, a healed tubercular focus in the right lung with pleural adhesions, and vegetative endocarditis of the mitral valve. The fourth case was already reported (case No 6, Raman, 1940). He was cured of his dermatitis and transferred to Mental Hospital where his condition gradually deteriorated, developed diarrhoea and died. The fifth case was a male aged 51 (case No 2), secondary pellagra associated with beri-beri. He died of septic complications and post-mortem showed septic broncho-pneumonia. The sixth case was a male aged 28. He was admitted with mental symptoms. He jumped from upstairs, produced a fracture of the skull and died. Post-mortem was not available. The seventh case was in a male aged 38 (case No 4), one of recurrent pellagra associated with mental symptoms. He died of septic complications and not of pellagra. Post-mortem was not available. The eighth case occurred in a male aged 40 (case No 6), a case of secondary pellagra associated with tuberculous ulceration of the caecum. The patient first showed slight improvement but gradually became worse and died. Post-mortem showed atrophy of the heart, congestion of the liver, broncho-pneumonia, gastritis, extensive tuberculous ulceration of the caecum with involvement of the glands and small areas of softening of both hemispheres of the brain. The ninth case occurred in a woman aged 45 years who was admitted with advanced pellagra with extensive dermatitis. The patient gradually became weaker and died. Post-mortem was not available. The last case was a male aged 20, a case of primary pellagra. In spite of treatment with nicotinic acid and liver extract, the patient's general condition gradually deteriorated and he died. Post-mortem showed atrophy of all the organs.

DISCUSSION

Casal (1735) described the dermal, gastro-intestinal and mental symptoms as one clinical entity and called the disease 'Mal de la Rose,' and later Frapolli introduced the name 'Pellagra.'

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The first case of pellagra that came to the notice of the author was in 1930, a case associated with mental symptoms, ever since the problem of pellagra has interested him

Geographical distribution—Pellagra has got a very wide distribution, and when one is on the look out for it, it may be possible to see it in every country. When it was first described in France, competent men refused to accept the diagnosis, and according to Stannus "many cases all the world over pass unrecognised and die undiagnosed". In India, as described earlier, the disease has been observed from various parts of the country. The highest incidence of pellagra was observed in Vizagapatam, an endemic area for beri-beri and other deficiency diseases especially riboflavine deficiency

Epidemiology—Patients admitted to the King George Hospital, Vizagapatam, came from the neighbouring Andhra Districts. The incidence of pellagra in relation with the total admissions and the number of patients admitted in the medical wards for 9 years are given below—(Table 3)

TABLE 3

| | 1939 | 1940 | 1941 | 1942 | 1943 | 1944 | 1945 | 1946 | 1947 | Total |
|-----------------------------|-------|-------|-------|-------|--------|--------|--------|--------|--------|--------|
| Total admissions | 7,098 | 8,314 | 9,245 | 9,330 | 12,230 | 13,383 | 13,300 | 11,104 | 12,302 | 90,901 |
| Admissions in medical wards | 2,604 | 2,458 | 2,809 | 3,470 | 3,497 | 4,414 | 3,805 | 3,400 | 3,745 | 30,252 |
| Number of cases of pellagra | 10 | 10 | 7 | 1 | 0 | 9 | 16 | 3 | 3 | 65 |

The incidence of pellagra was 0.25% of admissions to the medical wards, and 0.06% of the total admissions to the hospital

Age and sex incidence is given in the following table (Table 4)

TABLE 4

| Age in yrs | 0-5 | 6-10 | 11-15 | 16-20 | 21-25 | 26-30 | 31-35 | 36-40 | 41-45 | 46-50 | 51-55 | Above 55 | Total |
|------------|-----|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|----------|-------|
| Male | 1 | 0 | 4 | 5 | 5 | 20 | 15 | 20 | 4 | 8 | 1 | 3 | 86 |
| Female | 2 | 1 | 3 | 1 | 1 | 2 | 3 | 1 | 1 | 1 | 0 | 0 | 16 |
| Total | 3 | 1 | 7 | 6 | 6 | 22 | 18 | 21 | 5 | 9 | 1 | 3 | 102 |

The disease is present in infants, children, young adults and old people. The youngest patient observed in the present series was a child 9 months old, and the oldest a man of 70. The maximum number of cases occurred between 25 and 40 years of age.

Neither foetal pellagra nor pellagra in new born babies have been reported but cases have been observed in infants a few weeks old. Merck (1912) from an analysis of 4,862 cases found the maximum incidence between 20-50 years and 40 cases were observed below 5 years. Snyder (1912) reported a case observed by Savage in an infant of two months old. In this case the mother died of pellagra when the baby was six weeks old, but the dermatitis appeared only some days after the mother's death. Dodd (1941) reported that his youngest patient was a baby 10 months old.

The disease was more common in males and there was a definite preponderance of males (86 cases) over females (16 cases) in the ratio of 5.4:1.

Searcy (1907), Deaderick and Thompson (1916), Ruffin and Smith (1941), and Sundenstricker (1941) found greater incidence of the disease in females than in males. Harris (1941) found that alcoholic pellagra occurred more in males than in females. In infants and children, the ratio was the same as between boys and girls (Dodds, 1941). Thompson McFadden Pellagra Commission (1916) observed a ratio of 2.5 females to 1 male. Both sexes are affected but the ratio differs in different localities depending on the habit and occupation of the individuals (Manson-Bahr).

Seasonal variation—The seasonal incidence of the disease varies in different countries. In Vizagapatam, (Table 5) the cases usually occur in the cooler months of November, December, January and February. A few cases were observed throughout the year.

TABLE 5

| Seasonal variation of pellagra | | | |
|--------------------------------|----|-----------|-----|
| January | 20 | July | 4 |
| February | 14 | August | 4 |
| March | 7 | September | 7 |
| April | 4 | October | 5 |
| May | 3 | November | 12 |
| June | 4 | December | 18 |
| Total | | | 102 |

In America, pellagra is a disease of Spring and early Summer. Deaderick and Thompson (loc cit) observed the greatest incidence during the months of April, May, June and July, the maximum being in the month of May, and the minimum number of cases were observed in December. Sydenstricker (loc cit) from an analysis of 660 cases of pellagra found that it was seen throughout the year, but more than half of the patients were admitted during the months of May, June and July with the maximum incidence in July. The seasonal incidence of pellagra varies in different localities but is always the same in the same locality (Manson-Bahr).

Aetiology—In Italy and France, the incidence of pellagra considerably increased when maize was introduced. In the cases observed in Vizagapatam up to 1942 maize did not form a part of the diet, but after the introduction of rationing, maize was introduced as a definite article of diet, but the incidence of pellagra has not in any way increased. Stannus has collected seven cases from the literature in which pellagra has been produced by voluntary restriction of diet. One was in a young woman of 38 who took a faddist diet for 4 months and further restriction of diet to reduce her weight, one in a woman who restricted her diet, one in an old woman who restricted her diet to sweets and bread without any meat, eggs or milk, one in a Spanish labourer, and one in a tubercular diabetic with restriction of diet. A few more cases were observed in patients who followed a ketogenic diet. Stannus thinks that in these cases there was a deficiency of extrinsic factor, and in a few cases there was an associated deficiency of intrinsic factor.

Can pellagra be transmitted from one individual to another?—In the present series there were two cases in members of one family. In all other cases there was no evidence of any incidence of the disease in the family or the disease being transmitted from one individual to another. Bunivia (1808) injected the blood and secretions from pellagra patients

into volunteers without any success. Harris (1914) injected material (passed through Berkefeld filter and dissolved in normal saline) from cases that died of pellagra into 3 experimental monkeys. Two of these developed pellagra. The spinal fluid of a patient that died of pellagra was injected to a monkey and no symptoms developed. Unsuccessful attempts at the transmission of the disease to volunteers have been made by DeRolands (1828), McCafferey (1902), Lavender and Francis (1914) and Goldberger and Wheeler (1915). Although pellagra has been observed in mothers who were suckling the babies, there was no instance of the disease being transmitted to those babies. Harris (1941) reported two cases of pellagra in nursing mothers observed by Krauss showing exactly opposite findings. In the first case the child was six months old and breast fed, the mother was healthy, and the child developed pellagra at the age of six months. In the second case the mother had a very severe type of pellagra and throughout the active phase of the disease she nursed the baby and the baby was practically healthy. The experiments performed so far show that the disease cannot be transmitted from one individual to another.

Maize and pellagra —Lombroso (1869) and Fanzago (1807) formulated the theory that pellagra resulted by the use of maize. Guerreschi (1814) observed that fungus growth on maize was the cause of pellagra. Sette (1814) found that when potatoes were substituted for maize, pellagra disappeared. Lombroso (loc cit) observed, a certain toxin in maize called "pellagrazine" was responsible for pellagra. Valardani (1878) enunciated the theory that moldy maize was the cause of pellagra. Searcy (1907) eradicated pellagra in the United States when flour-bread and potatoes were substituted for corn-bread and grits. Stockman and Johnson found that experimental monkeys on maize diet, died from changes in the nervous system simulating pellagra. Harris (1940) has observed that the toxins in the corn (maize) may be a predisposing factor in the production of nicotinic acid deficiency which is essential for the production of pellagra.

The cases observed by the author in Vizagapatam where rice was the main article of diet till 1945 and where maize was not consumed by these patients at any time, showed that pellagra could occur in places where maize do not form an article of diet. After the introduction of maize in 1945 there was no increase of pellagra, in fact the number of cases were less than before.

Elvehjem and Krehl (1947) observed that corn contained a pellagra producing factor which could be prepared in high concentration and this substance "pellagragenic material" when given to experimental mice produced defective growth. Corn was deficient in the amino acid tryptophane and when this amino acid was added to the diet it produced the same effect as the nicotinic acid showing thereby that there was a direct relationship existing between nicotinic acid and amino acid tryptophane. They have also suggested that tryptophane may be a precursor of nicotinic acid. Kodicek et al (1947) found in experimental rats fed on 40% maize diet, defective growth curable by nicotinic acid and tryptophane. Indole-3-acetic acid when given in addition to extracted maize diet (with acetone water at pH 10 to remove the indole-3-acetic acid precursor) did not produce any retardation of growth.

Vitamin deficiency —Deeks (1912) and Funk (1912) suggested that pellagra is due to vitamin deficiency. It was originally called vitamin B₂ or vitamin G or pellagra-preventing-factor. Now it is called vitamin B₃ or nicotinic acid (niacin). Goldberger (1922) found that yeast prevented and cured 'black-tongue' in dogs, a disease similar to pellagra, and found that yeast gave complete protection against the development of pellagra. Vizagapatam is an endemic area for deficiency diseases. Beri-beri, pellagra and riboflavine deficiency are common and the number of cases of pellagra is much more than in any other endemic area of beri-beri in the Madras Presidency. Deficiency diseases are usually multiple. Beri-beri, pellagra, and riboflavine deficiency diseases due to deficiency of vitamin B complex may occur either singly or in combination and may also be associated with other vitamin deficiencies such as vitamin A or D. As suggested before (Raman 1940), the relative components of vitamin B complex in the diet such as B₁, riboflavine and nicotinic acid (niacin) may vary in different endemic areas.

Nicotinic acid (niacin) and pellagra —Elvehjem (1937) found that liver extract cured black-tongue in dogs and the factor that was responsible was nicotinic acid or the pellagra preventing factor. Swaminathan (1938) found very low values of nicotinic acid for maize. Sydenstricker et al (1939) observed the disappearance of stomatitis and glossitis of pellagra with the administration of nicotinic acid. Harris (1941) says that the quest for the essential factor in pellagra has ended, and deficiency of nicotinic acid (niacin) is the cause of pellagra. Aykroid and Swaminathan (1940) found the diets used by patients suffering from pellagra contained more nicotinic acid than the diet of an ordinary labourer in India. Now pellagra is treated with nicotinic acid and majority of the cases completely recover. In the earlier days of treatment, only smaller doses were used, and later it was found that larger doses are necessary in advanced cases especially those that are associated with mental symptoms. Cases have been recorded in which pellagra patients who did not respond to nicotinic acid were cured by liver extract (Harris, 1941). Sydenstricker (loc cit) reported a case of pellagra which was cured by liver extract after it failed to respond even to massive doses of 1,000 mg of nicotinic acid per day.

Himwich et al (1940) observed that the mental changes occurring in pellagra may be due to the break in the chain of carbohydrate oxidation due to nicotinic acid deficiency. Neuwahl (1943) observed a well marked fall of blood sugar in normal individuals after nicotinic acid, and the nicotinic acid given with insulin lowers the blood sugar much more than insulin when given alone. Marche and Delafarre (1943) observed that a large dose of nicotinic acid of 500 mg produced hypoglycemia. Bicknell and Prescott (1940) showed that some relationship existed between nicotinic acid and carbohydrate metabolism. They further observed that pellagrous patients are hyper-sensitive to insulin and hypoglycemia was easily produced in pellagrous patients rather than in normal individuals and this hyper-sensitiveness may persist even after the disappearance of symptoms of pellagra.

Elvehjem (1940) discussed the biological significance of nicotinic acid from experiments conducted in his laboratories and found that liver contained 1.2 mg of nicotinic acid per gm and the average daily

requirement of a man was 25 mg. Natural foods contained 1-100 mg % of nicotinic acid. He further observed that nicotinic acid deficiency does not result in the lowering of blood level of coenzyme I below the normal of 20-30 micrograms per 100 c.c. Excessive additions of nicotinic acid might temporarily increase the concentration of coenzyme I and concluded that the rapid response to treatment with nicotinic acid both in experimental animals and man was due to formation of coenzyme I when nicotinic acid was supplied. Van Veen (1940) found low nicotinic acid in the blood of cases of nutritional oedema and this was in no way connected with pellagra like symptoms observed in those patients, but found that it was associated with low cell volume. Naganna et al (1941) estimated the urinary excretion of nicotinic acid in pellagra and found that it varied from 0 to 3 mg. whereas in the normal, it varied from 4.8 to 6.1 mg. in 24 hours. Khorana et al (1941) estimated the nicotinic acid content of fish from Waltair coastal waters and found it to vary from 2.4 mg %, and prawns contained larger amount 4.8 mg. % Bean et al (1944) observed that an intrinsic factor produced in stomach interacted in some way with niacin and the frequent association of degenerative changes in the liver suggested that the liver played a part in the metabolism of niacin, and pellagra occurred when the body was unable to make an enzyme that contained niacin. Briggs et al (1945) studied the effect of restriction of nicotinic acid in two cases of pellagra and found that symptoms of pellagra did not develop although the experiments were continued for 9 weeks in one case and 42 weeks in the other, and suggested that the failure of development of pellagra may be due to intestinal biosynthesis of nicotinic acid.

Combined intoxication and vitamin deficiency—Megaw (1944) has suggested that deficiency of nicotinic acid alone was not the cause of pellagra but some other positive factor, probably intoxication, which was usually neutralised by nicotinic acid, may be present in addition.

Liver in relation with pellagra—The Illinois Pellagra Commission (1910) headed by Frank Billings found constant histological changes in the liver and they found that these changes were secondary to gastrointestinal infections. McCollum (1939) considers that liver has only very little power to store vitamins and a constant supply of vitamins is necessary to replenish the vitamin B complex in the liver and damage to the liver prevents the storage. Abnormalities in the function of the liver with or without pathological changes have been assumed to be an essential factor in every case of pellagra. Harris (1941) postulated the theory that there is an intrinsic factor in the liver and the deficiency of this is responsible for the production of pellagra and this opinion was based upon the facts, (1) that liver and liver extract cure pellagra and (2) that liver is a repository of all the vitamins. In addition, pathological changes in the liver have been observed in cases of pellagra. The important factor in the liver extract that cures pellagra is nicotinic acid and Sydenstricker found that normal liver contained 25 mg of nicotinic acid per 100 mg of the liver. In pellagra liver is deficient in nicotinic acid. Further he found that 92% of his fatal cases showed fatty degeneration of the liver.

Harris (loc cit) observed similarity of changes occurring in sprue, pellagra and pernicious anaemia, although these are three different clinical entities. The similarity in the pathology is usually manifested

by the changes that occur in the liver which consist mainly of fatty degeneration. Sprue, pellagra and pernicious anaemia may occur in the same patient and Harris records a case in which the patient suffered first from pellagra, later from sprue, and finally from pernicious anaemia. Mallow reported 2 cases of pellagra with pernicious anaemia, Alessandrini (1934) recorded a case of pellagra with pernicious anaemia and sprue, and Haden (1936) a case of pellagra with pernicious anaemia.

Recently a series of observations have been made on the changes in liver occurring in pellagra as demonstrated by liver biopsy. Gillman and Gillman (1945) studied the pathological appearances in 20 specimens removed by liver biopsy and the pathological changes observed were classified under 3 headings: (1) cases with considerable accumulation of fat in the liver cells, (2) cases with multiple coarse deposits of fat in almost all the cells, and (3) cases with dust-like particles of fat in the cells. In cases that showed accumulation of fat, treatment with vitamins was of no avail, and they observed that dried stomach had more beneficial effects in the treatment of such cases than liver extract. In another series, 23 cases of pellagra in children admitted in the Johnsberg Hospital during the years 1943-44 were investigated. Aspiration biopsy of the liver was performed in every case a few hours after admission and the patients were treated with vitamins by mouth as well as by injection. Biopsy of liver in these cases was done once in 7 or 10 days and the results of treatment with liver extract, and with dried stomach and HCl were compared. A study of the specimens in the earlier stages before treatment showed some amount of fat in the liver cells and this was a constant finding. In cases in which there was a great accumulation of fat, vitamins aggravated the condition. Liver extract and powdered stomach depleted the fat from the liver and this was associated with clinical improvement of the patient. Powdered stomach was found to have hypotrophic action in infantile pellagra.

Gillman et al (1945) examined sections of liver of 60 adult and infant pellagrins by fluorescence microscope and found a reciprocal relationship between the amount of fat in the liver and the amount of vitamin A fluorescence in the Kupffer cells. In the majority of cases, the amount of fluorescence was below the average. A porphyrin like fluorescence was seen in the liver cells of a few pellagrins. Frozen sections of the liver examined by ultra-violet fluorescence microscope showed intense scarlet-red fluorescence in 8 cases due to porphyrin. They observed that porphyrin like fluorescence can occur in acute stages and ultra-violet rays can produce recrudescence without producing any other clinical manifestation of the disease.

Sydenstricker (1941) succeeded in obtaining an extract prepared from the liver of a patient who died of pellagra within 2 hours after death. This extract was given to a patient suffering from pernicious anaemia and to 2 patients with a relapse of pellagra. The patient with pernicious anaemia showed rapid improvement while those with pellagra did not show any response whatsoever, showing that the pellagra preventing factor in the liver extract is different from that concerned with haematinic factor. Hansen-Pruss (1943) reported a case of sprue treated with diet and refined liver extract. He was readmitted seventeen months later with symptoms of pyloric obstruction and pellagra.

and was cured by nicotinic acid, showing that refined liver extract does not contain pellagra-preventing factor

Levulose tolerance test was done in 9 cases in the present series and it was normal in all the cases except one, and in that case it was done before and after treatment

LEVULOSE TOLERANCE TEST

A case of primary pellagra in a young girl aged 13 years

| Before treatment I | | | After treatment II | | |
|-----------------------|---------------------------------------|----------------|-----------------------|----------|----------------|
| 5-2-40 | | | 22-2-40 | | |
| | | Urino sugar | | | Urino sugar |
| 1 | Blood sugar before giving levulose | 120 mg% | | | |
| 2 | " ½ hr after 30 g | 152 " | | | |
| 3 | " 1 hr | 146 " | 28 g | 82 0 mg% | nil |
| 4 | " 1½ hrs. | 164 " | | 80 0 " | nil |
| 5 | " 2 hrs. | 141 " | | 69 0 " | nil |
| | | | | 67 0 " | + |
| | | | | 71 0 " | + |

The slight damage to the liver that was shown by the 1st test has disappeared as shown by the 2nd test after an interval of 17 days. In one case glucose tolerance test was done in addition and that was also normal. As all these cases were discharged cured, it was not possible to compare the post-mortem findings with the levulose tolerance test. This finding would show that the functional derangement of the liver was practically nil as far as could be judged by the levulose tolerance test, although post-mortem has shown in the majority of cases fatty degenerative changes in the liver.

Protein deficiency—All the patients were poor and some of them could not afford even a single meal per day. Here the deficiency was not only in the proximate principles of diet but also in the accessory factors. Is the deficiency in the quality or in the quantity of the protein that is responsible? In the present series, both were present. Whether there is any difference in the animal and vegetable protein, is not possible to say. Our patients reacted well both to animal and vegetable proteins. The Commission that investigated pellagra in Turkish prisoners in Egypt was of opinion that in pellagra there was a primary deficiency of "biological proteins". According to Wilson, the minimum amount of biological protein value required for an adult is 45 g and a diet whose value is below 33 g will precipitate an attack of pellagra. All proteins of proved biological value should contain a definite quantity of certain amino acids such as tryptophane and lysine. Goldberger and others believed that the amino acid deficiency was the cause of pellagra. There is certainly a defect in the absorption of proteins and especially when diarrhoea is present, defective absorption is a marked feature, but there is no evidence to show that there is a defect in digestion.

As reported earlier, estimation of blood proteins in 25 cases showed different types of albumin globulin ratio. In the majority of cases the total proteins were diminished and the diminution was mainly in the albumin fraction. In some cases there was an increase in the globulin. As a result of treatment with a liberal diet and liver extract, the proteins came up to the normal level, but in some cases the protein content remained low.

Gastric lesions in relation with pellagra—The studies of Johnson (1910), Boggs and Padget (1932), Mulholland and King (1938) and Bus-

man (1936) showed achlorhydria in the majority of the patients Sydenstricker (1941) summarised the results of gastric analysis done on 446 patients with histamine in some cases Achlorhydria was present in 77.3% of cases and in others the gastric contents were small with very little free HCl In patients with free HCl the mortality was 7.4% while those with achlorhydria the mortality was 19.5% Rubo (1941) from an analysis of gastric secretion from 342 cases of pellagra found that the secretion of fasting stomach was normal in 52%, reduced in 33.9% and was increased in 14% but in the later specimens the acidity was diminished in 95.6% Stimulation by alcohol or histamine increased the acidity in 0.9% and he concluded that achylia was a very characteristic and constant symptom, ran parallel with the clinical condition of the patient and was relieved by nicotinic acid Manson-Bahr (1945) found frequent achlorhydria or hypochlorhydria in 40% of cases

In the present series the gastric analysis was done in 17 cases, low acidity and absence of free HCl was noticed in advanced cases and as a result of treatment, the acidity increased, but in some cases the achlorhydria persisted The presence of pellagra in a patient with a duodenal ulcer confirmed by operation shows that pellagra may be present in individuals with high acidity

Petri, Norgaard and Bing (1938) produced clinical and pathological changes simulating pellagra in young pigs by gastrectomy In two of the cases already reported (Raman, 1940), one with gastro enterostomy and the other with gastrectomy done for duodenal ulcer, pellagra developed after the operation

Deficiency and anti-anaemic principle—Castle put forward the theory that pellagra, sprue and pernicious anaemia were due to a deficiency of the antianæmia factor A study of the blood pictures in the present series showed that macrocytic anaemia was present only in 17 cases (16.6%), and 5 of these showed in addition low acidity with the absence of free HCl In one case, gastrectomy for duodenal ulcer was responsible for the macrocytic anaemia In pellagra all the three factors, viz., deficiency of intrinsic factor, deficiency of extrinsic factor and defective absorption are present

Cases of pellagra especially primary pellagra with incidental disease were seen in which blood picture was either normal or showed evidence of normocytic anaemia That there was a deficiency in the anti-anaemic principle In these cases of pellagra was shown by the rapid response of these cases to injections of liver extract

Dermatitis of pellagra—Naked eye appearances in the earlier stages showed the condition to be inflammatory, and the final picture was one of degeneration and exfoliation Histopathology of the skin in the earlier stages of pellagra shows in certain cases slight inflammation of the dermis and infiltration with lymphocytes and mononuclear cells These inflammatory lesions are very small and may easily be missed if one is not on the look out for them Niles calls this condition erythema Is the dermatitis of pellagra due to trophic disturbances? The area of distribution does not correspond with the distribution of any of the peripheral nerves Stannus cites a case of a woman (case of Zeller) who had no dermatitis in the paralysed arm In the present

series of the author, there was bilateral symmetrical dermatitis in a case of hemiplegia. In two cases extensive exfoliation of the back with definite line of demarcation was observed and this may explain the theory of contact irritation. When a healthy individual was made to lie on the back as well as on a side on a cot spread with dusting powder, the same line of demarcation as observed in a case was produced. The theory of irritation does not hold good when patches develop in front of the thighs.

Exposure to sunlight or sun's rays has been advocated as the cause of dermatitis in pellagra since the patches occur over exposed parts in a majority of cases, but it cannot stand scrutiny as it is not uncommon to see dermatitis in parts not exposed to sun especially on the thighs, under the breasts and in the groins in women. According to other authors, the theory of irritation explains the unusual site of distribution. In Vizagapatam pellagra is a disease of the cold weather and people sit in the sun to warm themselves but they cover the hands and feet. So the question of exposure to sunlight alone cannot be the cause of dermatitis. One of my patients who was recovering from dermatitis was exposed to sun's rays, two hours a day for a week continuously and this did not produce any relapse.

Exposure to Roentgen-rays and ultra-violet rays—Harris (1940) has suggested the Roentgen-ray and ultra-violet ray exposure may have a role in the production of dermatitis. He reported the case of a woman who developed symptoms of pellagra after 72 hours of Roentgen-ray exposure for treatment of Hodgkin's disease, and was cured by liver extract in three days' time. One of the patients in the present series with tubercular abdomen was undergoing treatment with ultra-violet ray exposure of the abdomen. Two weeks later, the patient developed pellagrous dermatitis of the dorsum of both hands, and on subsequent enquiry it was found that the hands were placed well protected from the ultra-violet rays.

Porphyryns in relation to pellagra—Edgar and Lucas (1935) demonstrated that rats fed on a diet deficient in vitamin B₂ excreted large doses of coproporphyrins. Ellinger and Dojmi (1935) found increased excretion of porphyrins in cases of pellagra in Yugoslavia, the nature of the porphyrins was investigated and was found to be coproporphyrin I or III. In the present series porphyrins were estimated only in 2 cases and in both they were increased, but unfortunately second estimation could not be done after treatment. Beckh et al (1937) investigated the role of porphyrins in pellagra and found a close similarity between the symptoms of pellagra and those of acute porphyrinuria. In the majority of cases of pellagra there is damage to the liver and porphyrinuria is due to damage to the liver (Spies et al and Bicknell and Prescott). Further observations by Kark and Meiklejohn, Rosenblum and Jolliffe and Sydenstricker et al showed that increased porphyrins in the urine is not diagnostic of pellagra.

Mental symptoms in relation with pellagra—Bondurant (1910) considered neurasthenia as the earliest and the commonest symptom of pellagra. Partlow observed that actual psychosis and symptoms of a very severe type were the first clinical manifestations of pellagra, and some of these patients later on developed typical symptoms of dermatitis and diarrhoea. Pound (1928) noted that mental symptoms varied

from mild melancholia to mania, and the symptoms may simulate any mental disorder with one distinct feature *i e*, depressive character. Wilson (1940) observed slow cerebration, loss of memory, disorientation, toxic confusional psychosis, hallucinations, depression, occasional melancholia and a tendency to suicide as the main mental symptoms of pellagra. He quotes a series of 757 cases of pellagra of Miller and Ismail, of which psychosis of acute confusional or toxic variety and dementia were the commonest manifestations. Hardwick (1948) described mental symptoms in 10 patients of pellagra and found them to be schizophrenia, paraphrenia, dementia and imbecility. Meyerburgs (1945) observed two cases of senile psychosis simulating pellagrous encephalopathy that responded well to nicotinic acid therapy. Manson-Bahr (1945) has observed mental symptoms in one-third of all cases. Wilson (*loc cit*) has made a distinction between insane pellagra (pellagra developing in insane patients) and pellagrous insane (pellagrous patients developing insanity). He emphasized on this point and quoted cases in the mental hospital developing pellagra. Buchanan stated that some of the clinical manifestations resembled other degenerative lesions such as G. P. I. and the mental symptoms in pellagra were the same as those observed in other patients.

In the present series six patients showed mental symptoms such as loss of memory, incoherent speech, depression, melancholia and acute mania. One of these, already reported (Raman, 1940), had mental symptoms first and later developed pellagra (insane pellagra), and all others belonged to the group of 'pellagrous insane'. One patient had a suicidal tendency, jumped from the top floor of the hospital and committed suicide.

"Alcoholic Pellagra"—The name, "Alcoholic pellagra," was suggested in the literature especially from America where pellagra occurred in patients who were addicted to alcohol. Klauder and Winkelman (1928) found 97% of their patients were alcoholics, and Shattaek (1928) 78% of cases. Sydenstricker and Armstrong (1937) found only 8.8% alcoholics in a series of 440 cases. Spearman and Smith (1936) reported that alcoholic pellagrins rapidly recovered when alcohol was withheld and that symptoms reappeared when alcohol was reintroduced.

Ethyl alcohol produces acute or chronic gastritis associated with hypochlorhydria or achlorhydria and damage to the liver producing hepatitis or in rare cases cirrhosis of liver. Boggs and Padget (1932) suggested that alcohol destroyed the pellagra preventing factor or altered the function of the gastro-intestinal tract in such a way that the pellagra preventing factor was not absorbed. Harris (1941) has suggested that in alcoholic pellagra two factors are present (1) ethyl alcohol, and (2) deficiency of nicotinic acid. The damage to the liver in relation to pellagra is discussed separately. In the present series of the author, alcohol was consumed in large quantities by only two of the patients and a few others took toddy which contained only small quantity of alcohol. Toddy contains also yeast which is rich in nicotinic acid or pellagra-preventing factor.

Tuberculosis and pellagra—Green (1918) observed 25 cases of pulmonary tuberculosis in 131 cases of pellagra, and Sydenstricker et al (1937) 18 cases of tuberculosis in a series of 440 cases. Harris (1941)

observed that tuberculosis was usually associated with pellagra since malnutrition was a common feature of this condition. He also observed that in the majority of cases of pellagra, tuberculosis might occur as a terminal event. In the cases of secondary pellagra of the present series, the author observed tuberculosis in 6 cases, and the diagnosis was confirmed by post mortem in 4 of them. Fischer (1942) described two cases of pellagra in patients suffering from intestinal tuberculosis and suggested defective absorption as the cause.

Endocrines in relation to pellagra—Sutton and Ashworth (1940) treated two patients suffering from cachexia with anterior pituitry extract and noted improvement in the condition of the tongue of the patient and suggested a relationship between the anterior pituitrin and utilisation of vitamin B complex. In a later communication they reported 8 cases of pellagra treated successfully with anterior pituitry extract (Polyansyn) all of whom were treated for a long time without any improvement with nicotinic acid. In one of these cases, a low vitamin diet when taken with 2 c.c. anterior pituitry extract showed considerable improvement in the patient's condition. Burke and McIntyre (1938) found that when anterior pituitry extract was given, vitamin B deficiency diet did not produce any loss of weight in experimental animals. Brenneman found from experiments on chicks that anterior pituitry extract produced greater growth of the testes and combs in starved chicks than in controls. Sommer (1938) observed that starvation diminished lactogenic and gonadotropic hormones of the pituitry glands. Hundhausen (1939) found in rats that a deficiency of vitamin B₁ produced a decrease in thyrotropic and gonadotropic hormones. Starvation or vitamin deficient diet caused decrease in the anterior pituitry hormone and injections of anterior pituitry caused recovery from pellagrous symptoms especially in those that failed to respond to a liberal diet, liver extract and nicotinic acid. Wilson (1940) observed atrophy, haemorrhages, fatty degeneration and pigmentary changes with sclerosis in all ductless glands especially the suprarenals. Hellwig and Forman (1942) described in detail post-mortem appearances of a case of pellagra in a female of 38 years, showing atrophy of the zona glomerulosa and complete loss of lipoid in the cortex of adrenals, atrophy of the anterior lobe of the pituitry and hypertrophy of the islets of Langerhan. Quitter (1944) described a series of cases of pellagra in Rumania where maize was the common article of diet and where symptoms cleared up with the administration of sexual hormones.

Harris (1941) found only one case of pellagra in a series of 1,500 cases of advanced diabetes mellitus. He observed that low blood sugar was more common and quoted a case that was referred to him in which spontaneous hypoglycaemia was present. In the present series only 2 cases showed glycosuria and the glucose tolerance test in one of them showed advanced diabetes mellitus. Fasting blood sugar in this case was 298 and the maximum blood sugar was 480 mgs per 100 c.c. Fasting urine contained sugar. Another patient showed traces of sugar in urine but his blood sugar in a glucose tolerance test was normal. The last 3 specimens of urine showed sugar proving that the condition was only renal glycosuria.

SUMMARY

(1) A clinical study of 102 cases of pellagra (including the 37 cases already reported) has been made in Vizagapatam, an endemic area for pellagra, and where rice is the main article of diet. The introduction of maize as an item of diet since 1945 has not increased the incidence of pellagra.

(2) The classification adopted by the author in 1940 has been adopted and 70 cases of primary pellagra, 5 cases of primary pellagra with incidental disease, and 27 cases of secondary pellagra were observed.

(3) Pellagra occurred in 0.25% of the admissions in the medical wards and 0.06% of the total admissions in the hospital. There were 86 males and 16 females.

(4) Signs and symptoms of pellagra are described, and symmetrical exfoliative dermatitis with well defined margins was the main diagnostic feature of pellagra.

(5) Pathological and biochemical investigations revealed low blood proteins and different types of albumin-globulin ratios. Normal values were obtained after treatment. Detailed blood examination in 40 cases showed microcytic anaemia in 20, normocytic in 7, and macrocytic in 8, and normal blood picture in 5 cases.

(6) Gastric analysis was done in 17 cases and showed low acidity with the absence of free HCl. In advanced cases, the acidity increased in some after treatment while in others achlorhydria persisted.

(7) Treatment consisted in a liberal diet with milk, eggs, butter and liver soup, hydrochloric acid in cases that showed diminished acidity and absence of free HCl, and intramuscular injections of crude liver extract varying from 2 to 4 c.c. daily or on alternate days depending upon the seriousness of the disease.

(8) Nicotinic acid was given in larger doses of 100 to 1,000 mg per day either by mouth or by injection and rapid improvement resulted especially in cases showing mental symptoms.

(9) The aetiology of pellagra is discussed with special relation to maize, vitamins, nicotinic acid, liver, protein deficiency, gastric lesions, deficiency of anti-anaemic principle, alcohol, tuberculosis and endocrines.

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Note—Several other papers have been consulted and it was not possible to get the originals of some of the papers and only abstracts and quotations given by the authors quoted were available for reference

Description of the plates on pages 149, 150, 151, & 152

Fig 1—A group of 7 pellagra patients taken on 8-2-40 two more patients were in the hospital on the same day in advanced condition and could not be brought for the photograph

Fig 2—(Case 3) An advanced case of pellagra taken on 24-2-40 associated with avitaminosis B₁, showing exfoliative dermatitis on the dorsum of the hands and the feet

Fig 3—Same case as above taken on 5-4-40 showing improvement with liver extract and nicotinic acid therapy

Fig 4—The same patient taken one year later on 17-4-41 showing definite improvement in the patient's condition

Fig 5—(Case 6) An advanced case of pellagra showing extreme emaciation

Fig 6—Showing angular stomatitis and superficial glossitis. She had in addition, angular conjunctivitis associated with riboflavin deficiency

Fig 7—Same case as above showing the dermatitis on the dorsum of the hands

Fig 8—Same case as above showing dermatitis on the dorsum of both the feet

Fig 9—(Case 3) showing dermatitis on the dorsum of hands and oedema of the left hand

Fig 10—(Case 3) Dermatitis on the hands without any infection of the skin

Fig 11—Same case as above (Case 2) showing dermatitis on the dorsum of the feet smeared with petrol

Fig 12—Dermatitis on the dorsum of the hands showing exfoliation of the skin

Fig 13—Same case as above showing dermatitis on the dorsum of feet

Fig 14—Atypical pellagra showing dermatitis on the dorsum of the right hand only

Fig 15—Showing the dermatitis on the back of the leg and popliteal space

Fig 16—Radiological picture of the stomach after barium, taken on 27 1 39 showing atonic dilatation of the stomach

Fig 17—Radiological picture of the same case as above taken on 9 3 39 showing increase in the tone of the stomach after treatment

Fig 18—(Case 18) Infantile pellagra associated with congenital syphilis showing oedema and dermatitis on the face hands and the thighs

Fig 19—Same case as above, magnified view of the face

Fig 20—(Case 14) Infantile pellagra in a child aged 18 months. The dermatitis on the right hand is seen clearly but the left is very small

Fig 21—(Case 11) Pellagra in a child showing the front view. The dermatitis is seen in the groin, in the thighs and right round the ankle and the dorsum of the feet.

Fig 22—Same case as above showing dermatitis on the back of neck, on the gluteal region, popliteal fossa and the back of the ankle

Critical Notes and Abstracts

ABSORPTION, DISTRIBUTION AND EXCRETION OF STREPTOMYCIN—E K Marshall, Jr reported on the absorption, distribution and excretion of streptomycin in four female dogs and five male patients. The patients were free of hepatic, renal and cardiac disease. In the dogs, streptomycin was given in 10 cc of water intravenously in the course of three to four minutes, in man, intravenous streptomycin was given in 100 cc of saline over ten minutes.

The methods used for determination of streptomycin in plasma and urine were those described by Marshall, Blanchard and Buhle. All dosages and figures for plasma and urine are reported as streptomycin base. Urine was collected from the dogs by catheter, in man, by voiding. Blood was drawn from a vein, ovalated, and centrifuged at once to obtain plasma. The data obtained in this investigation were essentially in agreement with those obtained previously using the biological method of assay for streptomycin. In the dog nearly all of the streptomycin administered can be accounted for by excretion in the urine. In man, a considerable amount of the streptomycin is frequently not found in the urine. The renal clearance of streptomycin in both dog and man is less than the reported values for the glomerular clearance.

Unless streptomycin is bound to a great extent by the proteins of plasma, it would appear to be excreted by glomerular filtration alone. In both dog and man 50 to 80 percent of the amount of streptomycin injected was excreted in the urine in six to eight hours. The top level of excretion in the dog—80 percent—was much higher than in the male patients—68 percent. The percentage of excretion in 24 hours varied from 59 to 90 percent in the four male patients, and in two of the dogs, 86 and 88 percent, respectively.

(Marshall E K. Johns Hopkins University Medical School, Baltimore Maryland. *The Journal of Pharmacology and Experimental Therapeutics* 92-43-48 January 1948.)

CHRONIC RECURRENT PANCREATITIS—The series of 20 cases of chronic pancreatitis reviewed by Maimon and his associates comprised 12 men and eight women. In eight patients the distress had been present for less than a year at the time of initial observation, while in 10 symptoms had been noted intermittently for three to five years. One man experienced repeated attacks of abdominal pain for ten years and another for 30 years. The intervals between acute attacks of pain ranged from two days to six months. Mild transitory abdominal discomfort and vague digestive disturbances, however, were present almost constantly in the majority of patients.

Pain was the most frequent complaint. Dyspeptic symptoms such as bloating, eructation and vague abdominal distress were described by the entire group. In 16 post-prandial discomfort was considerable, and in 18 the ingestion of moderate quantities of food precipitated acute attacks of pain. Partial relief from pain was obtained by emesis in 10. Small frequent feedings tended to prevent the post-prandial distress. Loss of weight occurred in 12 patients. A history of recurrent jaundice with attacks of pain was obtained in eight cases.

The serum amylase content, determined in eight patients, was increased in three, normal in four and decreased in one. The oral test

for glucose tolerance, carried out in nine instances, yielded a diabetic type of curve in eight and a flat curve in one. Pancreatic calcifications were demonstrated roentgenologically in about one third of the cases.

Disturbances of carbohydrate metabolism were present in 10 of the 20 patients, a mild diabetic state being found in four and a more severe type in three. In the remaining three glycosuria was transitory. Steatorrhea was present in one-fourth of the group. Half of the patients had had previous surgical treatment, without relief of the abdominal pain.

The authors think that the possibility of pancreatitis must be considered in cases in which the patient continues to have attacks of pain simulating that of biliary colic after cholecystectomy has been performed.

The value of cholecystectomy has not been definitely established in the treatment of acute pancreatitis. Earlier reports indicate that cholecystectomy is of little prophylactic importance either in the primary or in the recurrent condition. Surgical intervention gives good results in patients with obstruction of the common duct and in those with constriction of the duodenum. Removal of ductal calculi frequently relieves pain, while steatorrhea may be favourably affected. An established diabetic state tends to remain unaltered.

(Maimon Samuel N., Dayton, Ohio, and Kistner, Joseph B. and Palmer, Walter Lincoln. *Arch Int Med* 81: 56-72, January, 1948.)

ORAL PROPHYLAXIS OF RHEUMATIC FEVER WITH PENICILLIN—Milzer and his associates direct attention to the fact that when military populations are undergoing mass chemoprophylaxis with moderate doses of sulfonamide drugs it has been shown that group A hemolytic streptococci readily become resistant to the drugs. While it is known that hemolytic streptococci may readily acquire resistance to penicillin in vitro and in vivo, the authors think that there have been no reports on the development of resistant hemolytic streptococci following oral prophylaxis with penicillin of either rheumatic fever or infections of the upper respiratory tract.

This paper is a preliminary report on the occurrence of penicillin-resistant strains of beta hemolytic streptococci in the throat culture of children with rheumatic fever who daily received 100,000 units of penicillin orally for at least five months to prevent recurrence of rheumatic fever. The authors felt that it is extremely important to report these observations on the development of penicillin fastness because of the present widespread usage of inadequate dosages of penicillin for prophylaxis or therapy in hemolytic streptococcus infections. Furthermore, development of numerous resistant strains obviously reduces the value of penicillin therapy and may even give rise to epidemics that could not be controlled with penicillin.

Throat cultures for alpha and beta hemolytic streptococci were made for 114 children with rheumatic fever. Sixty-four of the children were given a prophylactic oral dose of 100,000 units of penicillin daily for at least four months prior to culturing in order to prevent recurrences of rheumatic fever. The incidence of beta hemolytic streptococci in both groups closely approximated the normal carrier rate in healthy children as reported in the literature.

Eighty-two percent of the penicillin-treated and 40 percent of the untreated groups of children had beta hemolytic streptococci of signi-

ficant resistance to penicillin present in their throats. The occurrence of resistant strains in the untreated group can probably be explained by cross infection, since the two groups were in constant contact.

Inconclusive results were obtained on the development of significant penicillin resistance by alpha hemolytic streptococci. There was some indication that resistance develops somewhat more slowly than in beta hemolytic streptococci.

It is suggested that larger oral doses of penicillin be used for prophylaxis than is recommended in the literature in order to prevent the development of penicillin-resistant strains.

In an addendum the authors state that since this paper was submitted for publication we have found that 1,000,000 units of oral penicillin given daily for five days is usually ample to rid the throat of hemolytic streptococci and thereby avoid the possibility of penicillin resistance.

(Milzer, A. Kohn, Kate H. and MacLean, Helen, Michael Reese Hospital, Chicago, Ill. *Journal of A.M.A.* 136 530 538 February 1948)

Medical Notes & News

YELLOW FEVER VACCINE

The vaccine used in India is manufactured by the Rockefeller Foundation. The vaccine is also prepared by Messrs Burroughs Wellcome and Co., in England. It is also produced in South Africa.

The vaccine cannot be imported into India without the permission of the Director General, Medical Services, India. If any is imported by accident, the Director General must be immediately notified and permission for retaining it obtained. It is an offence to possess the vaccine without the permission or knowledge of the Director General.

At present the vaccine is donated to the Government of India by the Rockefeller Foundation. The Government then distributed it to the various provincial laboratories, which alone are authorised to vaccinate against yellow fever. The certificate of inoculation can be signed only by the director of the laboratory or by his nominee. For the Bombay province the Haffekine Institute, Parel, Bombay, stores and injects the vaccine.

The vaccine is not issued to medical practitioners. Under direction of the D.G. the vaccine is sometimes sent out to places where the need may arise, with all due precautions regarding its preservation. A record of all such vaccine sent and of all injections of the vaccine is kept by the Haffekine Institute. All yellow fever inoculations are given free. About a thousand inoculations are made every month.

The vaccine consists of the virus of the disease modified by numerous passages through the mouse, mixed with yellow fever immune human serum and then frozen dried and sealed in glass ampoules. Each batch is numbered. The vaccine must be stored at or below the freezing temperature. If exposed to a higher temperature it deteriorates rapidly so that it becomes useless in about three hours at room temperature. The vaccine loses efficacy even when kept at freezing temperature in about three months. Periodic checks are made of a batch by inoculating white mice, who develop a paralysis of the hind legs within 10 or 12 days if the vaccine is potent.

The vaccine comes in ampoules of 20 or 100 doses. It is a yellowish white powder. Before use the requisite quantity of sterile normal saline is added so that each dose is contained in half a ml. The solution must be used within three hours.

There is no fever or other reaction after the injections. Immunity is developed after 10-14 days and lasts for four years.

Reflections and Aphorisms

MEDICAL RESEARCH

"Harvey investigated the human body in health and disease, living and dead, and used animal experimentation to supplement his other studies. This is our birthright, derived from him, and we must not depute our proper tasks. A great need of the medical sciences in the present stage of their development and interrelation is a group of men, primarily clinicians, but fully accustomed by training and by daily experience to wrestle with scientific problems, men who, in place of relatively complete and accurate knowledge of some purely laboratory science, hold as the first part of their equipment intimate acquaintance with the relevant diseases as these are seen in living men, who have also acquired sufficient knowledge of related physiology and of general pathology, who have the aptitude to acquire quickly and well the necessary technical knowledge and skill, thus to enable them to grapple with the problem both in its detail and in its wide aspects, and to drive successfully to a practical goal.

But such work, it will be clear, requires not only ability, but it requires a man's full energy, it is not the type of work to which those busily engaged in practice can give themselves in leisure hours with full prospect of success. Physicians do not now live as Harvey did in times of easy and clinical activity, but in days of much heavier and more complex routine. So if the purpose in mind is to be brought to accomplishment it will be necessary to set free men having aptitude for the work outlined, to form a phalanx of trained clinicians who shall bring Clinical Science to a new pitch of scientific efficiency and hold it there."

SIR THOMAS LEWIS

CLINICAL PROGRESS

There are three chief ways in which clinical progress is achieved —

(a) the discovery of disease, that is the identification of disease and its natural history, (e.g. the description and definition, in recent years, of subacute bacterial endocarditis, of coronary thrombosis, and of hypertension)

(b) experimental work on clinical cases, (e.g. the action of digitalis in auricular fibrillation and in congestive cardiac failure), and

(c) the application of physiological ideas and discoveries in understanding the mechanism of disease, allowing us to interpret disease in terms of altered function, and ultimately, in controlling the disease, (e.g. the discovery that insulin enables tissues to utilize sugar, and that a substance in the liver may regulate the formation of red blood cells, influenced profoundly the progress of clinical medicine)

SIR THOMAS LEWIS

TALENT FOR RESEARCH

"The capacity to make great discoveries in medicine is an accident, a sport, and cannot be cultivated. It does not lie with honest toilers, or with the brilliant talent. No number of fellowships or scholarships can produce it. For a brief space of time, the spark inhabits a piece of human earth, and for that period a man becomes a god."

HARLEY WILLIAMS

The Indian Physician

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Original Contributions

ANTI-MALARIAL DRUGS OLD AND NEW WITH SOME OBSERVATIONS ON PALUDRINE IN MALARIA

by

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(From the Department of Pharmacology, Osmania Medical College, Hyderabad Deccan)

Introduction —The proper treatment of malarial infection is of utmost importance, because it affects nearly a quarter of the world population and kills about 3 million people every year. The bark of cinchona from which the alkaloid quinine is obtained has been in use for treating malaria from the early 17th century. The alkaloid quinine was isolated from cinchona bark by Pelletier and Cavintou in 1820. From this time up till the introduction of plasmoquin by a German chemist in 1926, quinine was the only effective drug against malarial infection. In 1930 another compound atabrin was synthesized and used in treating malaria.

In the last few years during the war extensive work has been done on the synthesis of new anti-malarial compounds possessing greater anti-malarial action and lesser degree of toxicity. As a result of these researches by the American and British workers paludrine, chloroquin, S N 13276 (pentaquine) and cam-aqi were synthesized.

The introduction of several new anti-malarial drugs necessitates the determination of their status as a therapeutic agent against malaria. With this point in view the author in this paper has given the relevant resume of the anti-malarial drugs and discussed their comparative value. The results obtained by the author with paludrine in malarial infection have also been included.

Classification of anti-malarial drugs according to their chemical structure

I *Iso-quinoline derivatives*

- 1 Quinine
- 2 Plasmoquin
- 3 S N 13276 (Pentaquine)
- 4 Chloroquin
- 5 Cam aqi

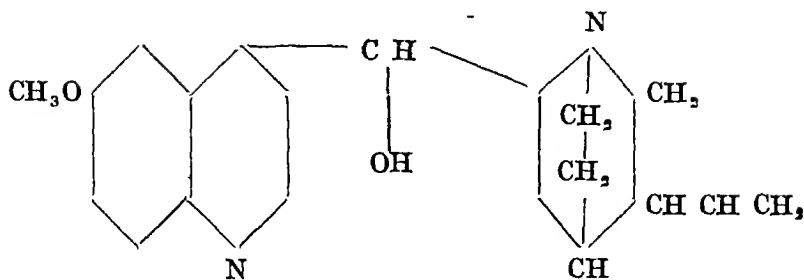
II *Acridine derivatives*

Atabrin (Mepacrine, Quinaerine)

III *Biguanide derivatives*

Paludrine

QUININE



Quinine is an alkaloid obtained from cinchona bark. The world yield of this alkaloid is about 600 tons and the whole of it is from the natural source. Quinine acts against asexual forms of all the varieties of malarial parasite.

I Insoluble salts

- (a) Quinine Sulphate
- (b) Quinine Tannate
- (c) Quinine Ethylcarbonate (Eu quinine)

The last one i.e. Eu-quinine is tasteless and so it is convenient for prescribing to children.

II Soluble salts

Quinine Bi-hydrochloride

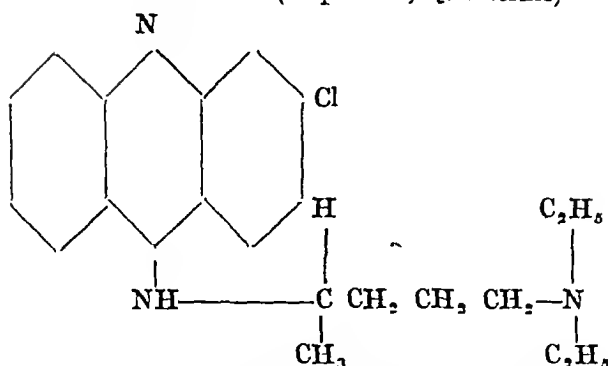
This salt of quinine is freely soluble in water and therefore is used for intravenous and intramuscular injections.

Mode of administration and dosage — Quinine should preferably be given by mouth unless there is some contra-indication such as vomiting or in cases of cerebral malaria when the drug is given intravenously. Oral route is the safest and satisfactory as regards rapid and adequate absorption. Intramuscular injections of quinine are painful and may cause tissue injury and abscess formation at the site of the injection. This route is only permissible when quinine could not be given by mouth on account of persistent vomiting. Intravenous route of administration is not without danger and therefore should only be reserved for the treatment of cerebral malaria cases.

The course of quinine for an adult suffering from malaria is 7 to 10 grains three times daily for 4—5 days. This should be followed by nightly 7 grains for 4 weeks. Quinine should be given in solution form and after food as it causes irritation of the stomach. In no case the daily dose should exceed 30 grains.

The common toxic symptoms and symptoms of idiosyncrasy are nausea, vomiting and tinnitus. Vomiting is some time persistent and in such cases quinine has to be administered parenterally. Quinine is comparatively cheaper and is very effective against malarial infection, but it has certain drawbacks namely, bitter taste, limited natural source and certain untoward side effects.

ATEBRIN (Mepacrine, Quinacrine)



Atebrin is a derivative of acridine, synthesized in 1930. It is of yellow colour and is soluble in water. Its action on malarial parasites is similar to quinine, but the relapses after atebrin are less common. It causes yellow colouration of the skin which is of no significance. Its rate of destruction in the body is slow and therefore the effects of a single dose last for many days.

Toxic effects—These are mainly on the alimentary canal and nervous system, and are as follows —

- | | | | | |
|----------|------------|------------|-----------------------|--------------|
| 1 Nausea | 2 Vomiting | 3 Headache | 4 Transient psychosis | 5 Depression |
|----------|------------|------------|-----------------------|--------------|

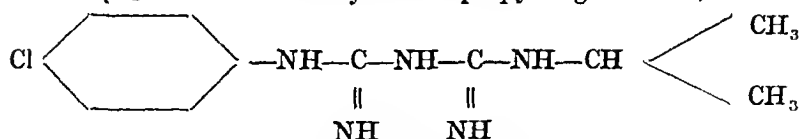
Dose — 0.1 G thrice daily for 5 days. In urgent cases atebrin musonate in a dose of 0.1 G per day may be given parenterally.

Advantages of atebrin over quinine

- 1 Fewer unpleasant side effects
- 2 A course of treatment necessary with atebrin is only a week compared to quinine which is several weeks
- 3 Fewer relapses occur after atebrin than after quinine

PALUDRINE (4888)

(N₁-Para-Chlor-Phenyl-N₅-Isopropyl Biguanidine)



Paludrine is a British discovery, synthesized and tested in avian malaria in 1945, and in the same year clinical trial was given in human malaria.

Chemistry — Paludrine in its chemical structure is very different from other anti-malarial compounds. It is a derivative of biguanide. It is a strong base so it forms salts with acids. It contains a chlorine substituted benzene ring and carries an alkyl group attached to nitrogen atom.

Mode of action — In avian malaria paludrine has been shown to have a powerful action on the blood forms, as well as on the exo-erythrocytic forms of malarial parasites. The exo-erythrocytic forms are found in the endothelial cells in the tissues and they occur as a stage between the sporozoites and trophozoites. These exo erythro-

cytic forms of parasites persist and act as a reservoir from which the parasites may be released to invade more R B Cs. The exo-erythrocytic forms have not been demonstrated in human beings but the occurrence of relapses is supposed to be due to their presence in the body.

Paludrine acts on the sporozoites of malignant tertian parasites in human beings and on the hypothetical exo-erythrocytic forms of malarial parasites which are supposed to be the cause of producing relapses.

Pharmacology — Given by the mouth paludrine is absorbed well from the gastro-intestinal tract. The concentration of paludrine in the red blood corpuscles is about four times that in the plasma.

The rate of excretion of paludrine is faster than that of atebirin. It has been found that very little paludrine could be detected in the blood even a week after receiving 1 G in two doses every day.

Toxicity — In some cases vomiting has occurred in the first two days of the treatment with doses of 500 mg twice daily. Australian workers have reported the occurrence of diarrhoea and haematuria in two volunteers who received a single dose of 1 G.

Malarial protection — Paludrine is a causal prophylactic i.e. it kills the malarial parasites before they enter the R B Cs. Paludrine when given in a single dose of 50—100 mg has been shown (Fairley, 1946) to afford complete protection against infection by mosquitoes carrying malignant tertian malaria, therefore it seems possible that the use of 1 tablet (100 mg) given once weekly in an endemic area would give complete protection against the malignant tertian infection. Paludrine also affords partial prophylaxis against benign tertian malaria. The symptoms of malaria can be kept in abeyance in all forms of malaria by a single tablet (100 mg) of paludrine given weekly.

Gametocidal action — Paludrine has no direct action on the gametocytes but in its presence even in a small concentration the gametocytes do not develop in the mosquitoes.

Dosage and method of administration — The question of dosage has not yet been settled, various workers have used different doses which vary from 10—1000 mgs daily. Macgiarath et al (1945) have used 5—750 mgs twice daily for 14—28 days in cases of benign tertian malaria and 50 mgs to 600 mgs twice daily for 14 days for cases of malignant tertian malaria. Another method which was adopted by them was the administration of a single dose of 300 mgs followed by 100 mgs weekly for 6 months. With this form of treatment they found that the parasite of the benign tertian and malignant tertian took 4—5 days to disappear from the peripheral blood. They also found that after the treatment of the acute attack of malaria the relapses could be checked indefinitely by giving 100 mgs of paludrine weekly.

Chaudhuri and Rai Chaudhari (1947) treated 80 cases of malaria with the following scheme of doses —

- | | | |
|---|--|--|
| <ul style="list-style-type: none"> (a) 100 mgs in a single dose (b) 300 mgs in a single dose (c) 100 mgs thrice daily for 4 days | } These could not check the relapses in many cases | (With these doses no relapse was observed during their stay in the hospital which was from 5—30 days). |
|---|--|--|

In the majority of their cases the parasites disappeared from the blood in about 3 days and in no case there was fever after the 5th day of the administration of paludrine

In November 1946, I was supplied with 200 tablets of paludrine by the Imperial Chemical Industries, Calcutta, for clinical trials. I tried the drug in about 20 cases of benign tertian and malignant tertian infection. Dosage employed ranged from 50 mgs to 300 mgs daily.

Method of administration of paludrine was as follows —

- 1 A single initial dose of 300 mgs followed by 100 mgs weekly for 6 weeks
- 2 Twice daily doses of 100 mgs for 14 days
- 3 25 mgs twice daily for 14 days was tried in one case and it was found to be as effective as the higher dose of 100 mgs given twice daily

*Results —*With the dosage mentioned above and the method used the temperature came down to normal in 1—3 days after the administration of paludrine, and the malarial parasites disappeared from the peripheral blood in 2—4 days. No relapse occurred during the stay of the patients in the hospital (stay-in period was 7—35 days). No toxic effects were noted with the dosage used in the treatment. Paludrine was found to have no effect on the gametocytes.

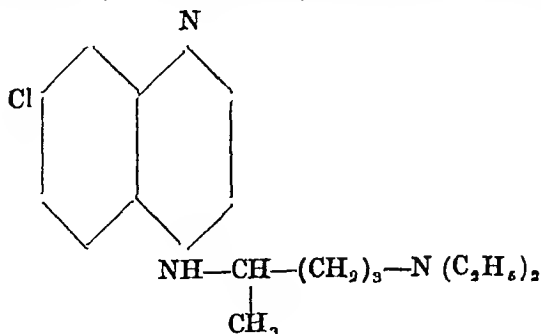
*Parenteral administration of paludrine —*Paludrine has been injected intravenously in a dose of 100 mgs without producing any toxic effect. It has also been used by this route for treating cases of cerebral malaria.

Paludrine has the following advantages —

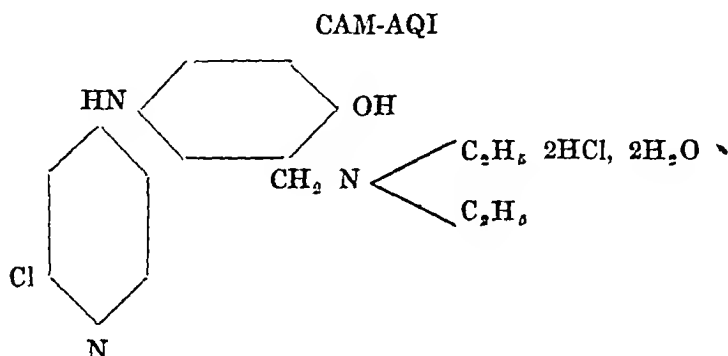
- 1 It is practically non-toxic
- 2 It reduces the relapse rate in benign tertian malaria, by acting on the exo-erythrocytic forms of the parasites
- 3 It is a complete causal prophylactic against malignant tertian and a partial casual prophylactic against benign tertian
- 4 It acts indirectly on the sexual forms of malarial parasites and thus inhibits their development in the mosquito
- 5 It has simpler chemical structure and so is easily made and less costly
- 6 It is colourless

CHLOROQUIN

(7-Chloro-4 (4 diethyl amino-1-methyl butylamino) quinoline);



It is a derivative of santoquin which was synthesized by the Germans before the war. Santoquin was considered by the German doctors to be little better than atebirin. In 1948 when the allies occupied Tunis they found santoquin left by the Germans. It was taken to Britain and America and several similar compounds were synthesized. Out of these compounds chloroquin was found to possess certain advantages. The action of chloroquin is similar to atebirin, but it does not colour the skin and it suppresses the infection with 0.25 G weekly doses whereas atebirin is needed in daily doses of 0.1 G for this purpose.



It is a new anti-malarial drug of quinoline series. Investigations made on this compound in the Parke Davis Research Laboratory showed that in avian malaria it is several times as effective as quinine and atebirin. It is absorbed from the alimentary canal rapidly and gives high blood concentration after absorption. The effective concentrations after a single dose of cam-aqi, are maintained for a longer time because the rate of its excretion is slow. Simeons and Chatre (1947) have used cam-aqi, in 314 cases of malignant and benign tertian infections, in single doses of 5, 7.5 and 10 mgs per kg body weight. Their results show that when the drug is given in a single dose of 10 mg/kg, no relapse occurred in the maximum observation period of 9 months, with doses smaller than 10 mg/kg relapses do occur. The temperature came down to normal in the average period of 48 hours and the parasites disappeared from the peripheral blood in an average period of 24 hours. Cam-aqi is a safe drug and it does not produce any toxic effects even with doses of 15 mg/kg. It has no effect on the gametocytes but it seems to suppress their formation probably by acting on the exo-erythrocytic form of malarial parasites.

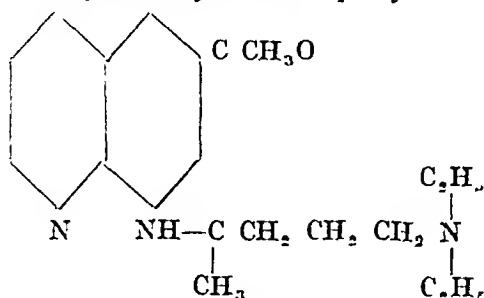
PLASMOQUIN

Plasmoquin was synthesized in 1926. It is of orange yellow colour and is insoluble in water. It has no action on the a-sexual forms of malarial parasites but it kills the sexual forms of all malarial parasites. This drug should be given with care because it sometimes produces serious toxic effects. Most common toxic symptoms are as follows —

- 1 Epigastric pain
- 2 Cyanosis, due to met-haemoglobinaemia.
- 3 Urticaria
- 4 Liver necrosis

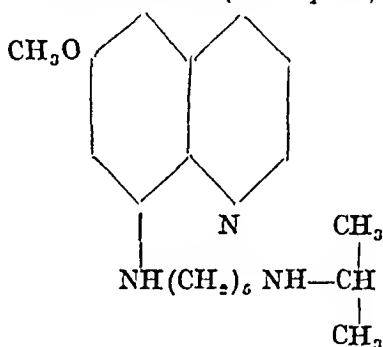
PLASMOQUIN (Pamaquin)

(6-methoxy-8 diethyl amino isopentyl amino quinoline)



Dosage and mode of administration —It is given by mouth in doses of 0.01G thrice daily for 3—5 days. It can also be given in combination with quinine. Atcbrin should not be given along with plasmoquin but an interval of not less than 2 days should be given after the course of atcbrin and before giving plasmoquin.

S N 18276 (Pentaquine)



It is a new compound of plasmoquin series synthesized by the American workers. Its action is similar to that of plasmoquin, but it is half as toxic as the latter. In man a thrice daily dose of 20 mgs of SN 18276 is as well tolerated as 10 mgs of plasmoquin administered in the same way. In combination with quinine it has completely cured volunteers in an American prison who were infected with the virulent strain of benign tertian parasite.

Conclusion —For a substance to be an ideal anti-malarial agent it is necessary that it should be effective in all forms of malarial infections, that it should possess a wide margin of safety and that it should be cheap and easily available. There is no drug available which will fulfil all the above mentioned conditions. Then we should see which drug is reaching the ideal. Paludrine and Cam-Aq appear to be superior to other antimalarial drugs so far discovered. Quinine the oldest is good in treating all forms of malarial infections when given in proper doses but in its case the course of treatment is longer and it has no effect on the gametocytes and it also produces some unpleasant side effects. Quinine is cheaper, but the treatment taken in a course which is longer costs the same as atcbrin.

these draw-backs still old is gold and as long as the new drugs are well tested and their defects known, one always would prefer to rely upon quinine for quicker and surer action.

Atebrin and Chloroquin are almost identical in their action, but the latter does not produce colouration of the skin and is a better prophylactic because it is only to be given in 0.25G dose weekly, whereas 0.1G of atebrin daily has to be given for this purpose. Paludrine is superior to quinine, atebrin and chloroquin because it is a complete causal prophylactic in benign tertian malaria. Moreover it prevents the development of gametocytes in the mosquito and reduces the frequency of relapses in benign tertian malaria by acting on the hypothetical exo-erythrocytic form of the malarial parasites. Paludrine has a simpler chemical structure, therefore it can be easily made at a cheaper cost, but its real value can only be established after its extensive clinical use.

Cam-aqi, which is a chemical compound of quinoline series seems to be very effective in curing malaria by a single dose. Some encouraging results have already been reported, it will be of great use in treating cases of malaria in the rural areas where administration of a course of treatment is usually not practicable in our country.

There are two drugs which act only on the gametocytes namely plasmoquin and SN 13276 (Pentaquine). Plasmoquin frequently produces dangerous toxic effects, the new American preparation (SN 13276) pentaquine, on the other hand, is as effective as plasmoquin but half as toxic, so that it can be safely administered instead of plasmoquin.

Now in achieving the radical cure of malaria one will have to use the combination of a drug which will act on the a-sexual form of malarial parasite with another which will act on the sexual form. In the past the combination of quinine with plasmoquin was used successfully in removing both sexual and a-sexual forms of malarial parasites from the body. Now that we have safer and better drugs at our disposal the following combinations are suggested.

- SN 13276 + Quinine
- SN 13276 + Paludrine
- SN 13276 + Chloroquin
- SN 13276 + "Cam-aqi"

Summary —

- 1 A resume of old and new anti-malarial drugs is given
- 2 Results of some observations on the use of paludrine in malaria are reported
- 3 The therapeutic value of different anti-malarial drugs in the light of their action and toxicity has been determined

Acknowledgements —

My thanks are due to Imperial Chemical Industries for supplying me with paludrine for carrying out the work when the drug was not available in the market.

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ON PROSTATE SURGERY

by

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Ambrose Pare was the first surgeon, to make a definite mention of hypertrophy of prostate. From the 16th to the 19th century is a long way but as it happened, that till Magill committed the so called great error, prostatectomy was unknown.

About six decades have passed since the historic accident which was responsible for the introduction of the surgery of the prostate. The distinguishing feature of the intellectual life of the last half century has been the progress of science of surgery. The advance has been revolutionary, almost passing belief. The operation of prostatectomy, which had been a formidable danger has become safe. This operation which had long been practised always with anxiety and often with remorse has grown more frequent and of unimagined safety. To-day with the development of transurethral technique and Millns' operation we are on the threshold of a new era in prostatic surgery. It seems that we are about to open a new and most momentous chapter in urology.

Hence it is logical at this juncture to glimpse at the past in retrospect and review our achievements and failures, particularly the failures as they shall be the stepping stones to our future success. The triumphant advance of prostatic surgery is due to the correct appreciation of the role of pre-operative treatment and post-operative care of the patient. The spectacular era of prostatic surgery when the gland was shelled out with dramatic movement within the twinkling of an eye, no longer exists. The flash of a genius without the requisite patience and deligence, is of no consequence in prostatic surgery. Today we face the solid realities and the treatment is well calculated and carried out with great deliberation. We use far greater efforts to improve the chances of the patient before the operation and to help him after the operation is completed. Many patients come to us when their condition is so gravely affected, either by the general advance of disease or due to sudden complications, that operation upon them cannot be contemplated without the deepest misgivings. Our first thought and all our efforts are and must be directed not so much to the operation itself as to the reconciliation of the patient. He must be restored to a degree of health and of resistance, which so far as it is possible, will make the operation safe.

Thus it is most vital for us to devote the greatest measure of attention to the preparation and after-care of patients. Surgery has been made safe for the patient, we must make the patient safe for surgery. A life is entrusted to our hands and it is for us to safeguard it. It is we who must take pains so to prepare or to rehabilitate our patient that the anxieties, the discomforts and the perils shall fall as lightly as possible upon one who at the moment is perhaps less than even able to bear them. The operation itself is but one incident no

A paper read before 75th meeting of Seth G S Medical College and K E M Hospital Staff Society on 11-10-47 with Dr R G Munsif in chair

doubt the most dramatic yet still only one in the long series of events which must stretch between illness and recovery

Hence it is the intention of this paper to put before the learned audience as complete a record as possible. Of 80 cases treated in the K E M Hospital during the period 1943-46, each case has been reviewed critically in the light of a proper master sheet and the aggregate results are summarised in the form of statistic table

TABLE 1
Age Incidence

| Age | No of cases | Remarks |
|-------------------|-------------|---|
| 40 to 50 yrs | 6 | The greatest incidence is in the 7th and the 6th decades. The average physical condition of patients at this age in this country being generally poor, far greater efforts are necessary in the preparation of the patients |
| 50 to 60 " | 25 | |
| 60 to 70 " | 31 | |
| 70 to 80 " | 16 | |
| above 80 yrs | 3 | |
| Total No of cases | 80 | |

TABLE 2
Average duration of stay in the Hospital

| Operation | No of cases | Remarks |
|--------------------|-------------|---|
| Freyer's 1 stage | 7 | This is a factor of great concern not only to the patient but also to us. Prolonged stay of a prostatic patient is a very common feature. Highest is 10 weeks, lowest is 4 weeks. |
| Freyer's 2 stage | 58 | |
| Thomson Walker's 8 | | This seems to be the feature of all transvesical operations and as long as they are practised there seems to be a very remote chance of improvement in this direction. |

TABLE 3
Symptoms

| Symptoms | No of cases | Remarks |
|--|-------------|--|
| 1 Retention | 56 | The most frequent symptom for which admission has been sought. In most cases there has been history of previous attacks with catheterization. In most cases it is and has been a late symptom indicating a profound upset of renal function. |
| 2 Frequency | 43 | Usually day and night both. |
| 3 Difficulty | 41 | Mostly during initiation of the act straining worsens the difficulty. |
| 4 Pain | 22 | Usually in the hypogastrium sometimes in the lumbar region. Rarely in pelvis and legs (cancer). |
| 5 Dribbling stream | 18 | |
| 6 Renal insufficiency | 2 | It seems that this symptom has been relegated to obscure place in history taking. Its importance is very great and bears a profound influence on the conduct to the case. |
| 7 Haematuria | 1 | |
| 8 Rectal | 2 | Both cases complained of blood in stools and in both of them the gland was malignant. |
| 9 Sex disturbances | | Surprisingly absent. |
| 10 Average duration of symptoms before admission | | 1 year and 1 month. |

Physical examination

1 Bladder was distended above the symphysis in 56 cases. Gross lesions of kidneys occur to be very rare.

2 Hernia was present in 7 cases. Some were operated previously. In one case patient developed retention after Herniorrhaphy and was found to be suffering from enlarged prostate for which he was treated later. Internal piles and prolapse were present in 8 cases.

3 Lesions of testes and epid. were found in 4 cases.

4 The examination of other systems and the general examination in general is very sketchy and in 20 cases only P R examination is mentioned.

At this age the affections of cardio vascular and respiratory systems are fairly common and greatly influence the treatment in all its aspects. The vagaries of physical examination in this respect cannot be compensated by anything in other fields. C V findings were positive in 8 cases and respiratory in four cases. 1 High B P 2 Angina 3 Bronchitis.

TABLE 4
Routine Examination

| Investigations | No of cases | Remarks |
|------------------|-------------|---|
| 1 Urine | | More than one third cases show urinary infection and show the importance of repeated urine examinations in all cases. It is not merely a routine but a necessity. |
| (a) Pus | 28 | |
| (b) Not examined | 20 | |

| | | |
|-----|----------------|----|
| 2 | Residual urine | |
| (a) | Examined | 4 |
| (b) | Not examined | 20 |
| (c) | Retention | 56 |

TABLE 5

Preliminary Investigations

| Investigations | No of cases | Remarks |
|---------------------------|-------------|--|
| Blood \ P \ | 56 | Blood \ P \ is the most common investg while blood pressure though simple has been neglected I wish to make a special reference to B P because the back pressure |
| Blood pressure | 23 | throws a great strain on circulatory system on the kidneys In fact it is this combined attack which spells disaster to the patient and hence it is not only rational but imperative that B P must be recorded at regular intervals during all the phases of treatment |
| Blood grouping | 20 | Many of the patients are ill nourished and anaemic and blood count seems to be a much needed investigation |
| Blood count | 3 | |
| \ Ray | 7 | \ Ray must be used more frequently The plain \ Ray of urinary tract for occul in Prostrate gladder and kidneys and of pelvic bones for secondaries is very necessary Both lesions are fairly common associated with the condition of enlarged prostate and the \ Ray may prove invaluable |
| Cystoscopy | 0 | |
| Urea concentration test | | It is necessary to know the exact degree of kidney function |
| Other investigations | | |
| (a) E. C. G | 2 | |
| (b) Stools | | |
| No investigations | 20 | This coldness shown with regard to preliminary investigation is not only gravely disappointing but beyond comprehension These investigations form a very important background in the management of a prostatic case and in fact they are the vital guides which indicate the course of the case either towards recovery or disaster Hence they are indispensable |
| Neglect of investigations | 28 | |

TABLE 6

Preliminary Treatment

| Nature of Preliminary treatment | No of cases | Remarks |
|--|-------------|--|
| 1 Care of bladder | | |
| (a) Gradual catheter decompression | 38 | |
| (b) suprapubic puncture | 3 | |
| (c) , cystostomy | 3 | |
| (d) Irrigations | 12 | |
| 2 Prophylaxis and treatment of urinary infection | 22 | This does not include the treatment with mist Buchu Co and Hexamine which were prescribed in almost every case |
| 3 Care and restoration of renal function | | |
| (a) Fluid therapy | 7 | Immediately after the institution of preliminary drainage the kidney functions, B P & general sense of wellbeing are depressed and fall to a lower level This is a critical point and a fluid therapy and F B sheet are absolutely necessary |
| (b) Fluid balance sheet | | |
| 4 General treatment | | |
| (a) Transfusion | 2 | |
| (b) Treatment of anaemias | 8 | |
| (c) Vit therapy | 8 | |
| (d) Respiratory infection | | |
| (e) Diet | | |
| 5 Prophylaxis or treatment of complications | | |
| Vaso-ligation | 24 | |
| 6 Nil preliminary trt | 50 | |

IMPORTANCE OF PRELIMINARY TREATMENT

It is impossible to over-emphasise the vital importance of preliminary treatment. It can safely be said that the battle of enlarged prostate is won or lost at two points one of which is the preliminary treatment. Gradual decompression is the first essential step in all cases with retention and large residual urine. It is with this step that kidney function and circulatory system are gradually restored to normal. In the present series according to records only in fifty per cent of cases gradual decompression was carried out. Preliminary treatment was either nil or neglected in 62.5% of cases. This is a matter for very serious consideration. If the high toll of mortality is to be stopped, it is imperative to maintain a very strict and high standard of preliminary treatment. At this stage I wish only to quote one case to illustrate this point—case No. 71. All the different items are of equal importance and none can be dispensed with.

PRE OPERATIVE CHECKING UP

It is important to estimate the improvement due to extensive preliminary treatment, before one operates on a prostatic case. If this is anywhere short of expectation it is wise not to proceed with the operation. The B.P. & N.P.N. must be fairly constant before the operation.

In the present series, the pre operative check up was almost absent as is shown by the following record—

| | | | | |
|---|-------------------|-----|-----|--|
| 1 | Blood N P N | 3 | 1 | Cystostomy |
| 2 | Blood Pressure | 3 | (a) | Anaesthesia local |
| 3 | Blood count | nil | (b) | nil finding (not recorded) |
| 4 | Urine exam | nil | | |
| 5 | G.C. | 1 | | No consistency in the record of these findings |
| 6 | Urea concent test | nil | (c) | Post cystostomy Check up |

TABLE 7

| Investigations | No of cases |
|---------------------|-------------|
| 1 Blood N P N | 40 |
| 2 " Pressure | 2 |
| 3 " group | 35 |
| 4 count | 5 |
| 5 Urine examination | 3 |

1. Post cystostomy treatment

In 81 cases (88.7%) no treatment except some mixt with buchu hexamine was given. Without post cystostomy no patient can be brought to a state when the case can be safely operated.

2. Prostatectomy

TABLE 8

OPERATIVE TREATMENT

| Operation | No of cases | Remarks |
|------------------------------|-------------|---|
| 1 Freyer's one stage | 7 | Without preliminary bladder decompression |
| 2 Freyer's 2nd stage | 58 | Most favoured operative technique |
| 3 J Thompsons Walker's op | 8 | |
| 4 Young's perineal operation | 2 | |
| 5 Cystostomy with vasolig | 5 | |
| Control of haemorrhage | | |
| 1 Irrigation | 12 | |
| 2 Gauze pack | 33 | |
| 3 Haemostat gag | 12 | |
| Difficulties in operation | 17 | 1 adherent prostate removed in bits |
| General anaesthesia | 11 | Mostly spinal anaesthesia was used |

TABLE 9

Post-Operative Care

| Nature of treatment | No of cases | Remarks |
|---|-------------|---|
| 1 Bladder irrigations | 59 | Most consistent feature of treatment |
| 2 Fluid therapy | 50 | These must be most consistent features of treatment |
| 3 Fluid balance sheet | 14 | |
| 4 Prophylaxis and treatment of renal fail | 18 | |
| 5 " urinary infect | 46 | |
| 6 " lung complication | 22 | |
| 7 General treatment | | |

| | |
|-------------------------|----|
| (a) transfusions | 75 |
| (b) Vitamin therapy | 12 |
| (c) Liver | 17 |
| 8 Surgical interference | 8 |
| 0 No treatment | 15 |

Only plain mixture was given. This is something which must be completely removed from future records. Such fatal items have no place in modern prostatic surgery.

VITAL IMPORTANCE OF POST OPERATIVE CARE

This is the most crucial point in the treatment of prostatic patient. Pre-operative treatment and post operative care represent the two phases of supreme importance in the management of the case. Post operative treatment must be carried out with the greatest diligence and sincerity. Its execution must be as thorough and ruthless as its planning. It admits of no compromise and no relaxation of rigid standards. All the 7 items enumerated in the table must be carried out in all cases. Then alone we can grasp the fruits of victory.

The importance of post operative care is illustrated by the record of case 50. Thus a perfect post operative treatment must be advised at all costs and is indispensable.

TABLE 10

| Post Operative Complications | |
|------------------------------|-------------|
| Complications | No of cases |
| 1 Haemorrhage | |
| (a) Primary | 0 |
| (b) Reactionary | 7 |
| (c) Secondary | 1 |
| 2 Renal failures | 11 |
| 3 Lung complications | 10 |
| 4 Urinary infection | 20 |
| 5 Suprapubic fistula | 10 |
| 6 Hiccoughs | 7 |
| 7 Pain | 3 |
| 8 Genital infection | 3 |
| 9 Urinary obstruction | 4 |
| 10 Urinary incontinence | 2 |
| 11 Distention | 4 |

TABLE 11

| Mortality | |
|---------------------------------|----------------------|
| Nature of operation | No of cases operated |
| 1 Freyer's 1 stage | 7 |
| 2 Freyer's 2nd stage | 58 |
| 3 Thompson Walker's | 8 |
| 4 Youngs perineal prostatectomy | 2 |
| Total mortality | 75 |
| | No of cases Died |
| | 12 |
| | 2 |
| | 1 |
| | 15 |

TABLE 12

| Cause of Death | |
|---------------------|--|
| Cause of death | No of cases |
| Renal failure | 7 |
| Circulatory failure | 5 |
| Lung complication | 2 |
| Urinary infection | 1 |
| | Remarks |
| | All these or at least most of them can certainly be prevented by patient and sincere effort directed towards preliminary investigation, pre-operative care and post-operative treatment. |

TABLE 13

Histological Reports

| Section report | No of cases | Remarks |
|------------------------|-------------|---|
| 1 Benign fibro adenoma | 50 | |
| 2 Malignancy | 8 | |
| 3 No report | 17 | In many cases the gland was adherent and removed with great difficulty. |

TABLE 14

Post Operative Check

| Investigations | No of cases |
|----------------|-------------|
| 1 Blood N P N | 0 |
| 2 " pressure | 2 |
| 3 " grouping | 1 |
| 4 " count | 2 |
| 5 Urine | 2 |

TABLE 15

Results

| Name of the operation | Discharged | cured | relieved |
|------------------------------|------------|-------|----------|
| Freyer's one stage operation | 3 | 4 | |
| Freyer's two stage operation | 32 | 14 | |
| Thompson Walker's operation | 2 | 4 | |
| Cystostomy with vasolig | | | 5 |
| Young's operation | | 1 | |

REMARKS

In conclusion, I venture to make the following tentative observations regarding the subject under discussion. During the critical survey of these 80 cases it was quite obvious that we have made a very definite and steady advance as the years rolled by but we are far away from our much coveted ideal.

There seems to be a great necessity of a skeletal scheme or master sheet, if we want our records to be comprehensive and reliable. They are far from satisfactory and it is impossible to assess our true position from them.

1 Due importance is not given to the recording of symptoms and signs of renal insufficiency. The examination of cardio-vascular and respiratory system is very casually done. These factors are of great importance, as the patient's age is much advanced and any mistake in this respect might upset the scales against the patient. Regarding the systemic examination and a diet suitable for a prostatic case, we should seek the opinion of non-physicians more often. It will give us an additional sense of security.

2 The routine examination of urine and estimation of residual urine require a far greater attention. The preliminary investigation should be more comprehensive and not limited to Blood N P N alone. A regular record of blood pressure, blood count, blood N P N at each stage must be maintained. Blood grouping must be indispensable routine. Routine X-Ray examination of urinary tract and pelvic bones would go a long way to help us. Urea concentration test if done as a routine, might in conjunction with the blood urea give us a more correct idea of renal function.

3 Regarding preliminary treatment, even at the risk of repetition I would add that nothing short of an ideal treatment, can be accepted. Gradual decomposition of bladder, prophylaxis and treatment urinary infection and renal failure, the fluid balance sheet, the treatment of lung infections, vitamin and liver therapy transfusions and a model diet, all have their essential part to play in this vital fight. In this joint and concentrated attack lies the secret of success. Its perfect execution or otherwise will decide the failure or defeat in each case. It holds a place of prime importance second to none, in the management of prostatic case.

The check up investigation at different stages of treatment are extremely important. A preliminary, a post-cystostomy and post-prostatectomy check up are the minimum requisites. These are the real indications to fitness or otherwise of the patient, any relaxation or weakness on our part, in this respect, will most summarily be fatal.

Regarding the operative treatment, record of findings during cystostomy and of the difficulties during prostatectomy should be kept more frequently. Post-cystostomy treatment is as imperative as the preliminary and must be perfect, as that is the only guarantee for a safe prostatectomy.

Now we come to another vital point i.e. post-operative care. Suffice to say that pre-operative and post-operative treatments are the two pillars on which the whole edifice of prostatic surgery is erected. Any tampering with these basic necessities is fatal and must lead to disaster. It is our sacred duty to see that the treatment is carried as near to perfection as the circumstances will allow. It is in this spirit alone that we can advance and score a lasting victory. These are the essential prerequisites of a much needed success and I am sure that we can reach it if we mean to.

Many post-operative complications can be avoided with a well planned treatment. Another important point I wish to stress is the follow up of patients after their discharge from the hospital.

So with all our short comings I feel certain that we shall rise to meet the occasion. The high mortality of 20 per cent is almost a challenge to surgery, which must be and I am sure, will be accepted. With some more efforts and stricter control of the treatment in its various phases, this institution can certainly produce not only comforting but brilliant results. It merely requires well planned concentrated drive towards eliminating complacency and achieving nothing short of ideal results. In our clear realisation of the importance of pre-and post-operative treatment lies the salvation of a prostatic victim. For us operation is an incident in the day's work but for our patients, it may be, and no doubt it often is, the sternest and most dreaded of all trials, for mysteries of life and death surround it and it must be faced alone. Those who submit to operation are confronted, after long and weary days or months of suffering, with the gravest issues, and far more often than we suppose they pass into the valley of the shadow of death. It is our privilege to give courage to those who need it. We have a higher mission in life and it is for us to see that we are worthy of it. The least that we can do for a prostatic patient is to redeem ourselves completely of our great responsibility by instituting a perfect and almost unchallengeable pre operative and post operative treatment. Rest lies in the lap of fate and I am sure it shall not be unkind to us.

DISCUSSION

Dr R J Manekshaw suggested a transverse incision in the skin to avoid persistence of suprapubic fistula.

Dr R H Karmarkar related his experience of urinary incontinence in two cases following operation.

Dr G M Phadke thanked the speaker for pointing out the high mortality in prostatic surgery. He suggested that an adequate pre operative preparation and post operative treatment would help to reduce the mortality. He added that post-operative incontinence was a temporary phase.

Dr K A J Lalkaka enquired about the use of testosterone propionate in the treatment of enlarged prostate.

Dr M M Pandya opined that Testosterone was not useful except in earlier cases. He pointed out some measures useful in reducing the operation mortality.

Dr S H Chitnis remarked on the occurrence of orchitis in three cases in spite of pre operative vasectomy.

Dr K G Munsif suggested the use of cystogram in the investigation of these cases and the use of suitable anaesthetics during the operation.

Critical Notes and Abstracts

HUMAN BRUCELLOSIS—Spink et al report a series of experimental and clinical investigations on the specific therapy of brucellosis with the sulfonamide drugs and antibiotics that have been carried out during the past ten years in the laboratories and clinics of the University of Minnesota Hospitals. The authors believe that the fundamental requisite of successful therapy for human brucellosis is that treatment should not only control the infection but the *Brucella* should be eradicated from the tissues, and thus therapeutic principle was the basis for seeking out a more satisfactory form of specific therapy.

Experimenting with chick embryos for the purpose of screening therapeutic agents, they found that when sulfadiazine and streptomycin were introduced simultaneously into the yolk sacs of infected embryos, not only was the survival rate greater but *Brucella* organisms were absent from the cultures of tissues in the majority of the embryos. It was demonstrated repeatedly that the combination of sulfadiazine and streptomycin has a much more effective antibruella action than either drug alone. In a typical experiment the livers of only 13 percent of the embryos contained viable *Brucella* organisms when the combination was employed in treatment, whereas *Brucella* organisms were recovered from 77 percent treated with streptomycin and 92 percent treated with sodium sulfadiazine.

Thirty-five human patients with active brucellosis were studied and observed by the authors, who directed therapy. Twenty of the patients received one of the sulfonamide compounds, particularly sulfadiazine; seven were treated with streptomycin, while nine had a combination of sulfadiazine and streptomycin administered to them. These cases of sporadic brucellosis were proved bacteriologically by isolation of *Brucella* organisms from the tissues or body fluids.

In the patients treated with sulfonamide compounds there was every indication that sulfonamide therapy did not eradicate *Brucella* from the tissues in well over one-third of the patients. Furthermore, recovery in some of the remaining patients might well have been independent of sulfonamide therapy and more directly associated with bed rest. Of the seven patients, all with infections due to *Brucella abortus*, who were treated with streptomycin, not one completely recovered following the administration of streptomycin. Nine patients with active brucellosis proved bacteriologically were treated simultaneously with sulfadiazine and streptomycin. Six of these patients had acute brucellosis, while three had the chronic form of the disease.

It was noted that the total doses of the two drugs used varied from patient to patient. While streptomycin was administered intramuscularly every six hours, the total daily dose was from 2 to 4 gm given over a period of seven to 25 days. With a few exceptions, the doses of sulfadiazine given orally were 4 gm initially and then 1 gm every four hours for three weeks. There were no complications due to the sulfonamide therapy. Streptomycin in a dose of 4 gm daily for 14 days caused a disturbing and persistent vertigo in one patient, but aside from this one case no toxic effects were observed.

The results of treatment in this group of cases were highly encouraging. The authors conclude that the combined use of streptomycin and

sulfadiazine in the therapy of patients with either acute or chronic brucellosis yielded more satisfactory results than previously obtained in the University of Minnesota Hospitals. The results were particularly encouraging since the treatment was effective in complications of brucellosis such as subacute bacterial endocarditis and spondylitis.

(Spink, Wesley W. University of Minnesota Hospitals Minneapolis Minn. Hall, Wendell H. Shafer, James M. and Braude, Abraham. *Journal A.M.A.* 136:382-387 February 1948.)

LYMPHOGRANULOMA VENEREUM—Costello and D'Avanzo report observations on 388 patients with lymphogranuloma venereum treated at the dermatologic wards at Bellevue Hospital from 1936 to 1945. Three hundred and seventeen, or 71.7 percent of the total number were men, while 71, or 18.3 percent of the patients were women, but there was a decided increase (39.8 percent) in the percentage of female patients and a decided decrease in the number of male patients in the last two years.

This increase in the number of female patients suffering from lymphogranuloma venereum may be due to the fact that these cases have accumulated because of the development of rectal stricture, since the disease is more chronic and of longer duration in women. Seventy-three percent of the patients were Negroes, the ages of the entire group ranging from 10 to 62 years. In 88.3 percent of the patients the genitals and inguinal lymph nodes were involved, while in 10.3 percent the rectum was involved. Sixty-five percent of the patients with rectal involvement were women. Seven and nine-tenths percent of the patients had rectal stricture, 75 percent of which occurred in women. Twenty-nine and four-tenths percent of the patients with genitoinguinal involvement had a primary lesion. Syphilis was an associated disease in 25.5 percent of the cases.

An intradermal test with Frei antigen was performed in 380 of the 388 patients studied. Of these, 365, or 95.5 percent showed a positive reaction, while in 17, or 4.5 percent, the reaction was negative. An intravenous test was performed with Frei antigen in 86 cases, the reaction being positive in 74 cases, or 86 percent. Five patients who had negative reactions in cutaneous tests had positive reactions in intravenous tests.

Since April 1938, use of the sulfonamide drugs has been the routine treatment for lymphogranuloma venereum. Sulfadiazine is less toxic and seems to be slightly superior to sulfathiazole. The period of hospitalization for all patients, excluding those with rectal involvement, averaged 21½ days. The authors conclude that the sulfonamide drugs and bed rest constitute the best treatment at present for the patients with early lymphogranuloma venereum.

Patients who have lymphogranuloma venereum with rectal involvement should have a course of treatment with sulfonamide drugs before operation is performed. In patients with proctitis the sulfonamide drugs are of definite value. Rectal stricture, which may necessitate surgical intervention, is the most formidable complication of lymphogranuloma venereum. Close co-operation of the dermatologist, proctologist, surgeon and internist is essential in the control and treatment of this disease.

(Costello, Maurice J. New York, N.Y. and D'Avanzo, Charles S. *Arch. Dermat. and Syphilology* 57:112-121 January 1948.)

NASAL HEMORRHAGE—Nervert and his associates report studies of use of ascorbic acid, prothrombin and vitamin K in patients suffering from epistaxis. Prompted by demonstration that prothrombin or ascorbic acid deficiencies are contributing factors in cases of late tonsillar hemorrhage, the authors studied ascorbic acid and prothrombin levels in 104 patients. It was found that 93 of these patients were deficient in ascorbic acid and/or prothrombin.

In 57 patients the nosebleed was traceable to one of the generally recognized local or systemic causes, and in 47 patients it was not. The percentage with both ascorbic acid and prothrombin findings normal was somewhat greater in the former group. Of 86 patients on whom follow-up was possible, 27 showed clinical improvement after treatment with 800 mg of ascorbic acid or 15 mg of "sinkayvite" (a vitamin K-like compound) or a combination of these amounts, daily for one to two weeks. Only nine showed no improvement.

The authors conclude that the extremely high incidence of ascorbic acid and prothrombin deficiency in a series of 104 consecutive cases of epistaxis and the gratifying clinical results attending the administration of ascorbic acid and/or a vitamin K-like substance in some of these cases suggest that vitamins C and K have a definite place in the management of nasal hemorrhage.

(Nervert Harry, Department of Otolaryngology, Columbia University College of Physicians and Surgeons, New York, N. Y., Engelber, Recha, Pirk, Leo A. Arch. Otolaryngology 47: 37-45 January 1948)

CLINICAL OBSERVATIONS ON STARVATION EDEMA

Berkman and his associates point out that during and after World War I it became possible to observe the effects of inanition on the human subject on a large scale. It was observed that starvation often was followed by edema, and in about half of the subjects examined the concentration of the serum proteins was decreased. It also was observed that under apparently identical circumstances normal values for serum proteins might be obtained and that definitely subnormal values were not necessarily associated with edema. Possibly because the first-mentioned observations were more in keeping with Starling's theory of formation of edema, emphasis was placed on the importance of the serum proteins in maintaining a dynamic equilibrium between the intravascular and interstitial fluids.

During and following World War II, however, emphasis frequently was placed on the absence of correlation between starvation edema and the concentration of the serum proteins. The plasma proteins were studied intensely by new and more precise physical and chemical methods. As a result, Starling's concepts have been thoroughly scrutinized and sometimes discredited.

Comparatively few cases of anorexia nervosa have been reported in which edema has been observed and values for serum proteins recorded. In some of the cases reported the coexistence of anemia and edema has been noted. The authors show that a review of the history on anorexia nervosa indicates that in this condition edema, anemia and decreased concentration for serum proteins may occur, but occur infrequently, and that the degree of emaciation is compatible in severity with that seen during wars and famine.

For a number of years the authors have been interested in the manner in which patients who were emaciated as a result of anorexia

nervosa have gained weight and in 1943 one of them called attention to a peculiar weight curve observed in a number of instances in which considerable weight had been gained. When an obese patient suddenly restricts his caloric intake, weight is lost rapidly during the first week. Subsequently, the weight remains stationary for a time and then decreases progressively. The initial rapid decline probably represents in part loss of extracellular fluid. The curve of weight gain in cases of anorexia nervosa appears to be the reverse. A satisfactory initial gain may occur for a week or even 10 days. This phase is followed by another which lasts a week or 10 days or longer, during which little if any weight is gained. At the end of this period, however, the patient, without any increase in caloric intake, will begin again to gain weight. It was suggested that the initial rapid gain in weight might be explained by retention of electrolytes and water and that during the phase in which no gain in weight occurred, excretion of water might be balanced roughly by an actual storage of flesh, which could be fat or muscle or both.

In 1945, one of the authors pointed out that patients who respond exceptionally well to dietary treatment may have edema of the feet and ankles at the end of the first week or 10 days of treatment, that the edema may not be noticed unless particularly looked for, and that it develops concomitantly with the initial gain in weight. In some instances the edema may be so extensive that the patient cannot wear the shoes that she has worn previously. In 1945 it was reported also that the values for serum proteins were normal in these cases.

Since, then, additional observations have been made in cases of anorexia nervosa. In these studies particular attention was paid to the level of the serum proteins and to the albumin-globulin ratio before and during treatment with a diet high in protein, calories and vitamins.

When cachexia is extreme, treatment must be cautious and undertaken with the understanding that little or no improvement can be expected for some time. Aggressive treatment of patients who have extreme degrees of emaciation may prove disastrous.

The basic principle of the dietary regimen used by the authors is a gradual increase in the caloric content and bulk of the diet. These patients either will not or cannot tolerate abrupt changes in their dietary habits. They frequently say, "My stomach has shrunk." Sudden increases in the bulk of the diet are followed by upper abdominal distress, lack of confidence and co-operation, and consequently failure.

The authors first make an estimate of the patient's caloric intake prior to arrival at the clinic. To this amount is added 800 calories. The patient is given a high protein, high-vitamin diet based on that number of calories (usually 1,800 to 1,500 calories or less) and is asked to eat everything served her. For the first few days the patient may complain of distress and a sensation of fullness. However, after several days these symptoms gradually become less. In five or six days the caloric content of the diet is increased by another 800 calories. For the next two or three days discomfort is again experienced, however, the symptoms again become less. This procedure is repeated until the intake reaches 3,200 calories.

Thirty-one patients having anorexia nervosa were studied at the Mayo Clinic with particular attention to the weight curve during dietary

treatment, the occurrence of edema and its relationship to the weight curve and the relationship of the edema to the concentration of the serum protein

In this group of patients body proteins have been severely depleted. The severity of this depletion is sometimes manifested in the level of the serum proteins and when it is, it implies that the body proteins and also the immediate source of the serum proteins have suffered.

No pitting edema was observed at any time in 15 patients, while in 12 patients edema was present on admission. Four patients acquired edema during treatment and in six instances pre-existent edema was increased following treatment. Among the patients who recovered from emaciation and may never have exhibited edema, the character of the weight curve suggested that a sequence of events occurred which was identical in character with those which occurred in patients who did exhibit edema.

In the treatment of anorexia nervosa by the method here employed, three phases can often be seen in the weight curve. Early in the course of treatment the weight rises rapidly, later it is maintained and a flattened curve results or it may even decrease. In the final phase there is a progressive rise in the weight curve and no edema is present. In the first phase edema may occur or increase if it has been present. In the second phase edema may persist or slowly decrease while the patient gains flesh. The weight of water lost is approximately equal to the weight of the flesh gained. In the third phase the disturbance in water balance has been corrected, water-logging has been overcome and a progressive gain in weight occurs. The weight curve may be misleading in evaluating the actual storage of flesh.

In severe cases of untreated anorexia nervosa values for the serum proteins more often than not were within the normal range, 6.0 to 8.0 Gm per hundred cubic centimeters.

In about a third of the cases values lower than normal were encountered. Values of less than 5.0 Gm per hundred cubic centimeters occurred in only one case. The level of the serum protein usually could not be correlated with the presence or absence of edema. With treatment the concentration of serum protein may decrease temporarily possibly because of hemodilution.

The levels of the serum proteins before treatment in the thirty-one cases studied were as follows: from 7.1 to 7.7 Gm per hundred cubic centimeters in four cases, from 6.6 to 7.0 Gm in 13 cases, from 6.1 to 6.5 Gm in six cases, 5.1 to 6.0 Gm in seven cases and 5.0 Gm or less in one case.

Another incidental but interesting finding was that 16 per cent of the 31 patients had a moderate or severe hypochromic anemia prior to treatment and in an additional two patients this type of anemia developed during treatment. The occurrence of edema did not appear to be contingent on the degree of anemia.

(Berkman John M., Mayo Clinic Rochester, Minnesota, Weir, James T., and Kepler, Edwin J. *Gastroenterology* 9: 357-369 October, 1947)

TUBERCULOUS MENINGITIS IN CHILDREN—Lincoln, Kirmse and De Vito report on treatment of seven children with tuberculous meningitis using *streptomycin* and *promizole*. The *promizole*

was administered orally at six to 12 hour intervals, so that the total daily dosage was 0.5 to 1.0 gm. This daily dose was gradually increased until the blood level of two to three mg per hundred cubic centimeters was obtained. The authors believe that a maintenance dose of one gm daily may be adequate after the first six months of treatment.

Dosage of streptomycin was quickly increased in the older and larger children to two gms intramuscularly daily in divided doses. Infants and smaller children received 0.5 to 1.0 gm intramuscularly daily. All patients received 0.1 gm of streptomycin intrathecally daily during at least the first week of treatment. An attempt was made to give intrathecal streptomycin for the first two months. In some cases treatment was given daily and in others on alternate days, depending upon the amount and number of toxic manifestations such as ataxia, nystagmus or transient strabismus. After two months of intrathecal therapy, a weekly, bimonthly or monthly spinal puncture was performed in order to judge the general course of the disease.

Of the seven patients, the first patient died after two months of treatment, six patients are living three to eight months after treatment was instituted. They are all normal mentally and have no neurologic sequelae except for a mild degree of strabismus in one case and transient coarse tremors of the upper extremities in another. Six of the patients had roentgen evidence of active primary tuberculosis and two of these had pulmonary miliary tuberculosis. Tubercle bacilli were found in the spinal fluid of five patients and in a sixth the bacilli were obtained by guinea pig inoculation from an accompanying bone lesion. No serious toxic effects of promizole were noted. All cases showed enlarged thyroid two to five months after treatment was begun. The only constant toxic reaction to streptomycin was ataxia which developed in the third and fourth week after institution of therapy. No evidence of auditory impairment occurred in any of the patients. The authors believe that their patients have not been under observation long enough to be reported as cured. However, they believe that the report of six out of seven patients so treated, none of whom show pronounced neurologic damage and all of whom are normal mentally, is a definite addition to increase of our knowledge of tuberculous meningitis.

(Lincoln Edith M., Bellevue Hospital New York New York Kirmse, Thomas W., and DeVito, Estelle. *Journal A.M.A.* 136:593-597 February, 1948.)

CARCINOMA OF THE LUNG—Lambert has presented a series of 70 cases of carcinoma of the lung surgically treated. His article stated that since the first pneumonectomy for carcinoma of the lung was successfully performed by Graham in 1933, more and more importance has been placed on early diagnosis of this condition. Medical treatment has nothing to offer, and as irradiation treatment therapy can be utilized only as a palliative procedure, surgery remains the only means by which the disease can be eradicated and cure effected.

The 70 cases presented which were surgically treated represent 20 percent of the cases of lung carcinoma encountered on the Chest Service at Bellevue Hospital, New York City. Only 7.2 percent of the total cases seen in this service were resectable. This low incidence of operability was associated with a discouragingly low record of five-year survival—only one case. The average duration of symptoms in patients coming to resection was more than nine months, due to failure of the

physicians to make a diagnosis and failure of the patients to appreciate the importance of early symptoms. A large percentage of patients who had resections died because of the presence of tumor beyond the resected area and too small to be recognised at operation.

The high incidence of fistulae and of pleural infection in resection cases indicated the necessity for improvement in operating technique and post-operative management. Careful dissection and skilful handling of the mediastinum have enabled more cases to be resected. As each surgeon's criteria of operability become more inclusive, a more radical approach is being adopted toward the disease. This approach is indicated as spread of the disease to regional lymph nodes and mediastinum has occurred following failure of earlier diagnosis. In these cases a radical resection with removal of lymph nodes and clearing out of the mediastinal glands up to the base of the neck becomes necessary. However, the surgeon's attempt to make up for failure of early diagnosis by employing radical pneumonectomy entails a much more formidable operation and a greater operative risk. The best way to lower mortality and increase survival rate is early diagnosis and early exploration which permits simpler pneumonectomy.

Operability of carcinoma cannot be predicted at bronchoscopy except that exploration is contraindicated where tumor can be seen to invade the trachea or extend to the opposite side. Rigidity of a bronchus may be due to the suppurative factor associated with the tumor as much as to the growth and does not preclude exploration. Dr Lambert believes that it is impossible to lay too much stress on the importance of roentgen ray interpretation rather than bronchoscopy or symptomatology for bringing about early exploration. Resectability is higher in cases with negative bronchoscopic findings. Until this fact is appreciated by the medical profession carcinoma of the lung will continue to have the hopeless prognosis that it has had in the past.

(Lambert, Adrian, Bellevue Hospital, New York, N. Y.: American Journal of the Medical Science 215:112 January, 1948)

Correspondence

DOSAGE OF PALUDRINE

TO, THE EDITOR, THE INDIAN PHYSICIAN,
Sir,

Certain changes in the dosage of 'Paludrine' for the treatment of malaria have been announced in the medical press this month and I would be glad of the hospitality of your correspondence columns in order that I may amplify this announcement for the information of the Medical Profession in India.

After the original clinical trials of 'Paludrine' by Professor N. Hamilton Fairley in Australia, by far the most extensive clinical trials were carried out in India and Pakistan under the auspices of the Malaria Institute of India in the years 1946-47. The results of these trials together with Professor Hamilton Fairley's published work led to the dosage recommendations contained in our present literature (leaflet Pal/1/June 1947 and brochure Pal/2 dated July 1947). Concurrent with clinical trials in India, however, investigations were carried out in many other countries, and, in the reports from Africa particularly, it was apparent that certain strains of the falciparum parasite in Africa required a heavier dosage of 'Paludrine' than was recommended in our literature. A few workers in India also were of the same opinion and felt that in certain cases of severe infection with some Indian strains of both the *P. falciparum* and *P. vivax* parasites, a heavier dosage was advisable.

Amongst the trials set up in Africa were trials on the prophylactic aspect of 'Paludrine' for protection against malaria in endemic and hyperendemic areas. Some of the individuals treated in these trials developed malaria in spite of taking one tablet (0.1 Gm) twice weekly at spaced intervals. Apart from these occasional 'break throughs' some doctors in Africa thought that a daily dose of one tablet (0.1 Gm) was easier for the individual to remember than a twice weekly dosage at evenly spaced intervals. They thought that taking one 'Paludrine' tablet (0.1 Gm) daily would be easier, and would obviate the occasional "break throughs" that had occurred in their trials.

In deference to these views, we have amended our recommendations for the treatment of malaria and these recommendations are as follows —

(1) For *Radical Cure*, 0.3 Gm twice daily for 10 days. In the case of severe infections the dose may be increased up to 0.5 or 0.6 Gm twice daily for the first three days. (2) For *Clinical Cure* that is to say, control of the acute attack of malaria a single daily dose of 0.3 Gm should be given until the fever subsides. This is the dose best suited for malaria arising in rural areas, (which has been called by some Indian writers "Village Malaria") where medical attention is not always easily obtainable. In the case of protection against malaria, however, although we have carefully considered the reports from Africa we do not think that we are justified in recommending the Medical Profession in India to adopt the daily dosage of one tablet (0.1 Gm) for prophylactic purposes. There are many well controlled Indian trials published, and unpublished, which show conclusively that on a dose of one tablet (0.1 Gm) twice weekly at evenly spaced intervals or three tablets (0.3 Gm) once weekly the incidence of malaria can be reduced to almost negligible proportions, provided the administration of the drug is regularly maintained during the transmission season. We therefore do not propose to make any alteration in our recommendations for prophylaxis and protection against malaria.

Full details of the new recommendations have been given in our advertisement in your journal and I am writing this letter in the hope that these remarks will be of interest to the Medical Profession when considering the new dosage. The matter has not been decided by my Company alone, and the Medical Profession in India may rest assured that the dosage we are now advising in our literature and advertisements has the support of the highest authorities on malaria, both in India and Pakistan and the U.K.

J. M. Mungavin M.B. B.Ch. (Cantab.)

Medical Service Department,
I.C.I. (India) Ltd.,
CALCUTTA-1

Medical Notes and News

The Bombay Medical Council has issued a New Code of Medical Ethics and the Warning Notice adopted by the Council in substitution for the old Code. The New Code printed below comes into force with effect from 1st July 1948.

Copies of the Code if required can be requisitioned from the Registrar, Bombay Medical Council, Swadeshi Mill Estate, New Queen's Road, BOMBAY-4.

CODE OF MEDICAL ETHICS

In taking up the medical profession you have selected one which is universally considered as the noblest, as its primary object is the alleviation of human suffering irrespective of gain.

It is your duty to do the best for your patients. You are not bound to treat each and every one who seeks your help, except in emergencies. You have the right to choose the patient and to lay down the limits of your service. But once you accept the charge it is your responsibility to exercise due care and diligence in the diagnosis and treatment, using the best means and opinions available to you. You cannot leave the patient without his consent except for very valid reasons. The discovery that the malady is incurable is not an excuse. Undertaking the care of a patient does not imply that you shall be blamed for not curing him. No blame will be attached if you have employed that skill and professional knowledge

which your other colleagues with a like qualification do in the community Naturally more is expected of one who claims to be a specialist

Your demeanour towards the patient should be courteous, sympathetic, friendly and helpful

While keeping the interest of your patients uppermost, you are not permitted to perform illegal operation or execute an illegal document or issue a false certificate

Knowledge of a patient gained in the course of examination and treatment is privileged and should not be disclosed without the consent of the patient or an order from a presiding judge in a Court of Law

To other members of the profession you owe a duty as a colleague You should never do anything which you would not like them to do to you Do not undertake to treat a patient who you know is being treated by another physician nor do or say anything that may make the position of your colleague awkward Most of the suits for malpractice arise out of such remarks Always respect opinions and differences of opinion

In practising your profession use methods of fair competition It is unethical to advertise yourself or solicit practice in any way

WARNING NOTICE

The Bombay Medical Council desires to bring to the notice of Medical Practitioners whose names are entered in their Register that if after due enquiry the Council finds them guilty of the following and similar unethical practices they are liable to be warned or have their names erased from the Register The Council is in no way precluded from considering and dealing with any form of unethical practice which may be brought before them although it may not appear to come within the scope of precise wording of any of the categories mentioned below —

PART I

Note —Any one found guilty of offences mentioned in this Part will be liable to have his name erased from the Register without any further warning

- 1 Immorality involving abuse of professional relationship
- 2 Conviction by a Court of law for an offence involving moral turpitude
- 3 Issuing in connection with various Government and Municipal Acts, sick benefit, insurance and kindred societies, passports, matters relating to armed forces, attendance in Courts of Justice, in the public services, or in ordinary employment, a certificate, notification or report which is untrue, misleading or improper
- 4 Withholding from the Health Authorities information of the Notifiable Diseases
- 5 Performing or enabling an unqualified person to perform an abortion or any illegal operation for which there is no medical, surgical, or psychological indication
- 6 Performing or enabling an unqualified person to attend, treat, or perform operations on patients in respect of matters requiring professional discretion or skill, or to issue certificates
- 7 Contravening the provisions of the Drugs Act and Regulations made under it
- 8 Selling scheduled poisons to the public under cover of his own qualifications, except to his patients
- 9 Disclosing the secrets of a patient that have been learnt in the exercise of his profession Those may be disclosed only in a Court of Law under orders from the presiding Judge
- 10 Soliciting private practice either by splitting fees or paying commissions to those who bring patients to him or by advertising by means of laudatory or other notices in the press, or, by placards or by handbills
- 11 Receiving commissions from surgeons, consultants, or from anyone to whom patients are referred to, such as a medical practitioner, a manufacturer, or a trader in drugs or appliances or a chemist or a dentist or an oculist
- 12 Advertising himself directly or indirectly such as through price lists or publicity materials of manufacturers or traders with which he may be connected in any capacity, though it will be permissible for him to publish his name in connection with the prospectus or directors' or technical experts' reports

PART II

- 13 Associating in professional matters with persons who do not possess a qualification registrable in India or who possessing such a qualification have been struck off the respective Registers for unethical practices

14 Writing prescriptions in secret formulæ

15 Keeping an open shop for the sale of medicines

16 Publishing or sanctioning the publication in the lay press of reports of cases treated or operated on by him or of any certificates for drugs, foods, appliances, sanatorium used by him or of any laudatory statement about himself or his address and telephone number unless he has changed his office or has resumed practice after a long interval in which case the notice should not appear more than twice and in not more than two papers, or inserting his name in the telephone directory in a special place by paying special rates

17 Contributing to the lay press interviews, letters regarding disease and treatment which have the purpose of advertising himself and soliciting practice. It shall be open for him to write to the lay press under his own name on matters of public health interest and general articles which will promote hygienic living or deliver public lectures with the same purpose. Till such time as local medical publications offered the desired publicity it shall be open to medical associations, hospitals and other bodies to advertise the name of the lecturer and his subject in the non medical press provided that such a notice has already been sent to the medical press for publication, where available

18 Attending a patient who is under the care of another practitioner

19 Attending on his own a patient who has been seen by him before in the capacity of a consultant during the same illness

20 Removing the patient in the absence of the attending physician to a hospital or a nursing home or transferring him to the care of his assistants by a consulting practitioner

21 Doing anything that means unfair competition

22 Talking disparagingly of his colleague who attended the case before him or attends with him at a consultation

23 Examining and reporting on employees at the instruction of the employer without previously intimating the regular medical attendant of the employee of his commission and giving him the option of being present

24 Using an unusually large sign board and writing on it any thing else other than his name, qualifications obtained from a university or a statutory body, titles conferred by Government and the name of a speciality he practises. The same should be the contents of his prescription paper, which may in addition contain address and telephone numbers. Appointments held now or before should not be mentioned either on the board or on the prescription paper

25 Refusing to attend on a patient who has been under his care unless (1) he finds that the patient and his relatives are nonco-operative, or (2) his fees are not paid, or (3) another practitioner is consulted without his knowledge

Note—The foregoing do not apply so as to restrict the proper training and instructions of *bona fide* students or the legitimate employment of dressers, midwives, dispensers, surgery attendants and skilled mechanics under the immediate personal supervision of a registered medical practitioner

SUGGESTIONS

The following suggestions may be useful in medical practice —

1 You should strive to maintain your medical knowledge at a high level by regular reading, by attending refresher courses whenever available, and by attending and taking an active interest in the meetings of your local medical society and conferences. Add your knowledge and experience to the common pool and thus contribute to the advancement of medicine

2 Never forget that the doctor by virtue of his profession is given a high place in Society. Study and assist in solving the civic and political problems of your Society but not by neglecting your patients and profession. Do nothing to forfeit the esteem and the confidence of your fellowmen. In thought, word and deed be a gentleman

3 Every practitioner may charge a fee at each examination of patient and he should encourage the latter to get the medicine from a qualified pharmacist, as the small profit accruing from dispensing medicines to his patients is not adequate remuneration for his professional services

4 In serious illness, in doubtful conditions, in operations of a mutilating or destructive nature upon an unborn child, in operations which may vitally affect the intellectual or generative functions of the patient always ask for a consultation

5 At the consultation there should be a free exchange of opinion. These discussions should be held without the presence of the patient or his relative. An agreed statement or otherwise should be communicated to them by the attending physician,

6 Before performing an operation, obtain in writing the consent from the husband or wife, parent or guardian or the patient himself as the case may be. In an operation which may result in sterility the consent of both husband and wife is needed.

7 Do not undertake more work than you can conveniently manage. If you are running a dispensary practice avoid over crowding by not calling patients twice or every day, unless it is essential to do so. To many, medicines may be given for three days. Charge your fees every time you examine a patient. If you agree to attend a woman in her confinement you must do so and the excuse that at that time you are engaged with another patient and could not leave, is not valid.

8 Though your fees may vary according to the means of your patients, do not attend patients free of charge unless they are poor. There are hospitals for the poor.

9 If your patient needs investigation and technical assistance which is beyond you and beyond the limits of the purse of the patient, do not delay in referring him to a public institution.

10 Do not claim to be a specialist unless you have put in a good few years of study and experience or have a special qualification in that branch. Once you say you are one, do not undertake work outside your speciality even for your friends. Live and let live.

11 If you are running an institution for a particular purpose such as a mental home, a sanatorium, a house for cripples, blinds etc., you may advertise it in the lay and medical press. The advertisement should not contain anything more than the following information —

Name of the institution, the address and the approach, the types of patients admitted, facilities offered and the residential fees. The name of the Superintendent may appear in the Medical Press. It is not advertisement to celebrate the annual function of your institution and invite your friends to it, such a function may be reported in press.

12 While it is scientific to offer a good prognosis if one's findings lead to it, it is unwise to guarantee a cure.

13 Prescriptions, x ray plates,* investigation reports are the property of the patient.

14 When issuing a medical certificate always enter the identification marks of the patient and keep a copy of the certificate.

15 Do not publish photographs or case reports of your patients in any medical or other journal in a manner by which their identity could be made out without their permission. Should the identity be not disclosed his consent is not needed.

16 If you are running a nursing home* and if you employ assistants to help you, the ultimate responsibility rests on you.

17 Do not accept appointments, whether honorary or salaried in institutions where the practice is to "split fees" for visits and injections between the practitioner and the institution.

* About the legal ownership of x ray films there is still difference of opinion and the statement by the Bombay Medical Council that the films are the property of the patient will be questioned by many. This question of legal ownership of x ray films is recently answered by a writer in the British Medical Journal (May 20, 1948, p. 1059) as follows:

The question "Who is the legal owner of x ray films?" has never been finally settled. It is discussed at length with many illustrative case references by D. Harecourt Kitchin in his *Legal Problems in Medical Practice* (1936 pp. 127-30) and it was also the subject of an article which appeared in the B. M. J. of Jan. 13, 1934 (p. 80). It is generally agreed from the medical point of view that the films belong to the radiologist; they are an indispensable part of the material on which he founds his opinion. If the patient pays him a fee, this is in respect of his opinion and not in consideration of the handing over of the films. If the films are so handed over and the radiologist is afterwards sued for giving a negligent opinion, he would be unable to defend his interpretation of the films unless they were handed back to him. The German Röntgen Society issued a declaration in 1912 to the effect that it considered that all films, prints, diagrams, tracings etc. prepared by the radiologist were to be regarded as his property just as the histological preparations of a consulting pathologist remain his property on which he bases his opinion of the nature of the material submitted to him for examination. The practitioner who refers the case to the radiologist is entitled as a matter of courtesy, to inspect the films.

There are several decisions in American Courts (quoted by Kitchin) which go to show that the x ray films are the property of the radiologist or of the hospital in which such an examination is made and that it is just as necessary that the film shall be retained by the practitioner in charge of the case as that he should preserve the temperature charts and other case records. In determining any question of ownership of the films the Court has regard to the nature of the contract, and will not generally speaking, infer without express evidence that there is any contract to hand over the films to the patient who pays his fees for expert advice and not for the documents or other material on which that advice is based. —Editor, *The Indian Physician*

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FLATULENCE

by

GEOFFREY EVANS, M D F R C P

A healthy digestive tract contains gas. Some gas is normally passed *per anum* in defecation and some may be passed in sleep, and also perhaps in the day. About 500 c c is said to be evacuated in this way during 24 hours.

Air in Stomach

In the ordinary way air is swallowed with food, and a little with fluid. It lies in the fundus of the stomach under the left dome of the diaphragm. On x-ray examination it is well seen in the upright posture, but when the subject lies down the air spreads out under the anterior wall of the stomach and does not show on the screen or in film. Dr A. E. Barclay¹ has suggested that air in the stomach forms a buffer or air-cushion which saves the organ from undue shaking, especially when it is full of food.

Air in Bowel

X-ray examination generally shows gas in the colon, but there is none in a healthy small intestine. Most of the gas found in the bowel is nitrogen. The oxygen and carbon dioxide of swallowed air are more readily absorbed and so nitrogen is left.

Varieties of Flatulence

When the stomach or intestines are distended with gas there is complaint of wind or flatulence. This distension may be due to excess of swallowed air as result of eating in a hurry, or of excessive swallowing due to chronic post-nasal catarrh, or to salivation due to dental carries or oral sepsis.

Aerophagy

Air may be swallowed as result of habit, and this may be initially due to some gastric or abdominal discomfort or disorder. It may happen that an individual has gastric catarrh and an irritable state of the stomach. The swallowing of air affords temporary relief, the stomach becomes distended with air; it is uncomfortable and belching wind relieves the discomfort, and so the habit of aerophagy is formed. Persons who swallow air should be advised not to belch, because without knowing it they swallow air when they think they are bringing it up.

Air-sucking

Air-sucking² is distinguished from aerophagy in that air is sucked into the stomach through an open oesophagus by the creation of a negative pressure in the abdomen. The abdominal wall is fixed, the chest is expanded and the left dome of the diaphragm is drawn up, thus creating a negative intra-abdominal pressure. Air-sucking is a neurosis and most commonly occurs in hysteria.

Absorption of Gas from the Blood

Intestinal flatulence may be due to absorption of gas from the blood. For instance, at operation an isolated and empty length of bowel may quickly fill with wind when it is clamped at either end. Again, in intravenous pyelography the preliminary radiogram may be normal, but after intravenous injection of the dye subsequent radiograms may show the intestines distended with gas, presumably due to the stimulus of the injection. Emotional shock may have the same effect.

Borborygmi

An amount of gas that is little in excess of normal may cause symptoms when the digestive tract, or some part of it, is out of order. An atonic state of the stomach is the cause of the sometimes loud rumblings heard in the upper left abdomen and known as borborygmi. Borborygmi are under the person's control in that the noise can be produced at will, but it can be prevented only by keeping the body in a certain position. Borborygmi are produced by gas bubbling through from a lower locus to an upper locus of an atonic stomach, and this occurs with every expiration. In a normal stomach with good muscle tone this does not happen, because the stomach contracts with the descent of the diaphragm in inspiration and lengthens in expiration.

Gurglings

Gas bubblings from one part of the intestine to another are distinguished from borborygmi in that they are irregular and not repetitive, as are borborygmi, also they often occur in the right iliac fossa at the ileo-caecal junction or in the left iliac fossa.

Cascade Stomach

In cascade stomach (cup and spill) there is often a sensation of a lump, fullness or pressure in the region of the xyphoid cartilage. This sensation may be relieved by belching and so may lead to aerophagy. Bockus³ gives a good description of cascade stomach and remarks that it is difficult to say whether aerophagy is the cause or the result of it.

Aerogastric Bloqué

Excess of gas in the stomach may be the cause of severe pain in the left hypochondrium when, on account of oesophageal spasm, it cannot be expelled. This condition is known as aerogastric bloqué.

Symptomatology

The usual local symptoms caused by flatulence are belching, abdominal distension, discomfort or pain, borborygmi, gurgling, passing wind *per anum*. The remote symptoms are palpitations, irregular

heart and cardiac consciousness, headache, pain in the back in the right and left lumbar region. There is, too, an emotional reaction, varying in kind and degree according to the individual's constitutional make-up.

Actiology

The causes of flatulence are so many and varied that their complete and concise classification is difficult. An attempt has, therefore, been made to classify flatulence under the main headings of Obstruction, Irritation and Lack of Tone.

Either (1) obstruction or (2) irritation of any part of the digestive tract below the oesophagus is a cause of flatulence. These two conditions are often coincident because obstruction causes catarrh or inflammation. In acute gastritis there may be constant belching of foul smelling gas, and in chronic gastritis the epigastric discomfort, often worse after food, may be relieved to some extent by belching. This may lead to acrophagy. Pyloric obstruction, with delayed emptying of the stomach, causes excessive fermentation and putrefaction of gastric contents and is another cause of offensive eructation, although this is not often complained of by the patient. In carcinoma of the stomach there may be flatulence upwards. The gas is generally odourless and is sometimes foul. In general terms organic disease of the stomach is not an important cause of flatulence and this is especially true of peptic ulceration.

(1) Intestinal Obstruction

Whether partial or complete, intestinal obstruction is a most important cause of abdominal distension and flatulence. The first symptom of a carcinoma of the pelvic colon may be the passage of wind *per anum*. The fact that any kind of obstruction in the intestine, *wherever it may be*, may cause flatulent distension is illustrated by the case of a woman who was diagnosed as having partial obstruction of the small intestine and who, at operation, was found to have two strictures of the ileum. A large gall-stone¹ was held up behind the proximal stricture. The gall-stone was removed, but neither stricture was dealt with in any way because both strictures allowed the passage of the little finger. This operation was performed by Sir Thomas Dunhill in 1935. The patient was cured of her abdominal symptoms for 3 years, when she began to get colicky pains again and abdominal distension. It was thought that she had intestinal obstruction. This diagnosis was confirmed by finding a severe state of Fibrous Anus. The stricture at the anal orifice was gradually dilated during the following months by the use of rectal bougies, and the patient, now aged 70, was cured for the second time of her abdominal discomfort and flatulent distension.

Constipation

Perhaps the most interesting cause of flatulent distension due to *obstruction* is constipation of the kind which results from a failure of the evacuating mechanism, namely, pelvic-colon or rectal constipation. Rectal constipation is easily diagnosed, if not by the patient,² at least

¹ In this remarkable case biliary colic was suspected before operation and cholecystography was done. The gall bladder filled and emptied normally with dye. The stone removed from the small intestine was analysed by Dr H. E. Archer and proved to be a gall stone.

² Whether it is in the rectum or pelvic colon constipation may be diagnosed by the individual by the sensation of incomplete evacuation. It may be this daily slight and vague discomfort which is responsible (and sometimes justifiably so) for the regular laxative habit.

by the doctor, by a rectal examination after defaecation. Pelvic colon constipation on the other hand may require a barium meal or enema x-ray examination for its diagnosis. It is not generally known that incomplete evacuation of the pelvic-colon, when defaecation takes place, may be the cause of flatulent distension. It is of interest too that this distension may be chiefly or entirely of the caecum or ascending colon. This may lead to the diagnosis of appendicitis (wind in the caecum), or cholecystitis (wind in the hepatic flexure). In this connection it is important to remember that pelvic-colon constipation may be difficult to diagnose and is perhaps the commonest reason for the excessive use of laxatives.

(2) *Intestinal Irritation*

Irritable states of the small and large intestine—enteritis and colitis, whether specific or non-specific, local or diffuse, are all conditions liable to be associated with excessive wind in the intestines. The habit of taking laxatives regularly and in excess, that is to say in quantity sufficient to determine the evacuation of a loose stool, is one of the commonest causes of flatulence.

Fatty Diarrhoea

Normal bowel contents may be bowel irritants when present in excess in a part of the bowel unaccustomed to them. Thus in all forms of fatty diarrhoea there is excess of fat in the large intestine. A quantity of fat normal to the small intestine may be an irritant to the large intestine and cause flatulence, distension and colicky pain.

Intestinal Carbohydrate Dyspepsia

Similarly, starch which is not digested, sets up intestinal carbohydrate dyspepsia, of which Hurst⁴ said that the chief symptom is abdominal discomfort caused by distension of the colon with gas. Cellulose is digested in the caecum and ascending colon. In those who habitually take too much laxative, or who have loose stools for any other reason, the cellulose reaches the distal colon incompletely digested, irritates it and causes flatulence. Such persons often cannot, therefore, take green vegetables and salads. Under the same heading falls allergy, for in some people there may be hypersensitiveness in the digestive tract to certain foods. One of the diagnostic symptoms of intestinal allergy is flatulence.

(3) *Lack of Tone in the Organs of the Digestive Tract Acute Dilatation of Stomach*

The outstanding example of this condition is acute dilatation of the stomach, especially as seen after abdominal operations, and occurring sometimes as a complication of other trauma and of acute infections. It is often associated with aerophagy. A chronic atonic stomach has already been discussed in describing borborygmi.

Hirschsprung's Disease

Hirschsprung's disease is an extreme form of congenital atonic colon, in which considerable accumulations of gas may be present. Classical examples of this condition are relatively uncommon, but

moderate degrees of atonic colon, aggravated by fatigue or illness, are quite often found in patients with abdominal symptoms of obscure origin are subjected to x-ray examination as a matter of routine

Congestive Heart Failure

It is probably also due to a lack of tone in the digestive tract, or perhaps to sub-clinical alterations of intestinal rhythm, that flatulence and flatulent distension are common symptoms of failure of circulation in the portal area, whether due to congestive heart failure, portal obstruction (as in cirrhosis of the liver) or arteriosclerosis of the mesenteric vessels. In some patients it is remarkable what a sensitive index to circulatory efficiency is provided by this symptom of gastric or intestinal flatulence

Reflex Flatulence

It probably belongs to this same order of events, namely, variations of intestinal tone, that organic and functional diseases elsewhere in the body may cause intestinal flatulence. Examples of such conditions are renal calculi (the only symptoms of which on occasion are intestinal), gall-stones, and arthritis or injuries to the spine

Emotional States

Alvarez⁵ has called attention to the importance of emotional states as a cause of intestinal flatulence. It is curious that quite a minor emotional disturbance may determine sudden abdominal distension which is, in some cases, complicated by belching, and in others by the passage of wind *per anum*. These symptoms may be quite transitory. When such a condition is brought on by fear (examples of this were common during the air raids) one sees the truth of the phrase "He got the wind up"! Under these circumstances the gas would seem to be absorbed from the blood

Fatigue States

It is common knowledge that abdominal distension often occurs towards the end of the day in persons who are living beyond the limits of their physical or nervous strength. But it is not generally known that in such individuals intestinal activity may not, on account of fatigue, be sufficient to perform its task during the night's so-called rest

Right Ilac Fossa Pain

In consequence there may be an accumulation of gas in the caecum and ascending colon which causes pain in the right ilac fossa, or the gas may accumulate in the distal colon and cause a headache. In either event, the symptom may be relieved on occasion by taking a large dose of caffeine citrate, namely, 5, 7½ or even 10 gr. The object is to prescribe the maximum dose of caffeine citrate that the individual can tolerate. The combination of caffeine citrate with an equal quantity of aspirin may be more effective than the caffeine salt alone. The individual is advised to lie quietly in bed for three-quarters of an hour after taking the caffeine and aspirin. The evidence that these symptoms are due to distension with gas is the sensation of the movement of wind in the bowel within 10 to 15 minutes of taking caffeine citrate

In the case of gas in the caecum it may be recognized as passing through the transverse colon, then in stages through the distal part of the bowel, and then finally evacuated *per anum* with complete relief of symptoms within 30 or 45 minutes

Treatment

It will be obvious from what has already been written that the treatment of flatulence should be based on the indications provided by its aetiology *Flatulence is the most sensitive index of the integrity (both functional and organic) of the digestive tract*. Its aetiology should always be first considered in terms of organic disease, especially new growth, inflammation and catarrh. In the second place conditions which affect the digestion and assimilation of normal food, together with the possibility of allergy, should be considered. Finally, account is taken of general physical and emotional states, such as fatigue and exhaustion, excitement, irritability and fear, and their effect on the digestive tract in causing hypertonic or atonic states, or in other cases causing absorption by the bowel of gas from the blood.

Post-operative Flatulence

This condition, which is often troublesome, and may be painful, and even on occasion a serious complication of post-operative recovery, has a varied aetiology. Thus it may be due to pre-operative treatment, and to the bowel having been emptied of food residues too completely. Laxatives in excess are a cause of flatulence, because the colon cannot contract down completely as can the small intestine, and must, therefore, contain gas if it is completely emptied of semi-solids. Further, laxative in excess may disturb normal peristalsis, and so irritate the bowel as to determine the absorption of gas (this is the presumption) from the blood. Handling of the bowel may cause accumulation of gas. Following abdominal operations, nervousness, nervous exhaustion, and subclinical congestive cardiac failure are other factors. On occasion distension and abdominal pain are due to the close relation between bowel function and the tone and activity of the voluntary muscles of the thorax and abdominal wall. An example will make this plain.

A young woman suffered abdominal distension and severe pain following a pelvic operation. The pain was so severe that for 5 days she had had to have heroin to relieve it. On the evening of the fifth day, when I saw her, a slightly rising temperature (99.2) suggested the possibility of a pelvic clot, which it was thought might be becoming infected, and penicillin or even another laparotomy seemed to be possibilities. She was sitting up in bed, restless with pain, and asking for sedatives to relieve it. The lower thorax was contracted and the abdomen was distended. The patient was persuaded to lie on her back and to put her legs out straight. She was then quietly persuaded to do slow deep breathing to expand her lower thorax, hands, on the lower thorax moving with respiration drew her attention to the part of her chest which required expansion. The bandages were left *in situ*, and she was given gentle massage, first in the flanks, which were hardly tender, and then as the pain eased off the abdominal wall was gently massaged towards the wound. Within 10 minutes she was largely relieved of her pain, and she required no further injections of heroin. /

The explanation of this kind of so called flatulence is the disordered movement (partly lack of movement) of the thorax, diaphragm and abdominal wall, as result of which the rhythm of intestinal movement is so far disturbed as to lead to, I believe, disordered intestinal contraction and perhaps to pockets of wind. The distension is certainly not mainly due to accumulation of wind because by the above treatment relief is obtained without the passage of flatus *per anum* or the belching of wind. The psychological effect of the quiet normal breathing, the relief from discomfort, and the efficiency of the treatment, give the patient confidence and restore peace of mind, which is, of course, one of the most important aspects of treatment. In conclusion, it is interesting that in the case referred to the temperature was normal next morning*.

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MODERN LABORATORY METHODS IN THE DIAGNOSIS AND CONTROL OF TYPHOID FEVER

by

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Two recently introduced laboratory methods have proved to be of great service to the epidemiologist who is called upon to investigate cases and outbreaks of enteric fever (1) typing of Typhoid bacilli by means of V₁ bacteriophage and (ii) V₁ agglutination tests as an aid to diagnosis and to the detection of chronic typhoid carriers

TYPING OF TYPHOID BACILLI BY THE V₁ BACTERIOPHAGE

Craigie and Yen (1938 a, 1938 b) made the important discovery that strains of the typhoid bacillus can be divided into a number of well defined types according to their sensitiveness to types-specific anti-V₁ Bacteriophages. Until then the typhoid bacillus had been regarded as a single species without varietal subdivision. The great advance due to the work of Craigie and Yen was based on their observation of a special adaptability possessed by one particular anti-V₁ Phage. When this phage was propagated on typhoid strains isolated from different outbreaks, preparations of bacteriophage were obtained which had developed a high degree of specificity for the particular strain on which they were grown. Strains that were related epidemiologically were invariably found to respond in an identical manner to the different phage preparations, and on this basis Craigie and Yen identified a number of distinct V₁-phage types of *Bacterium typhosum*.

The Phage type of strain is for all practical purposes a permanent character, and typing of the typhoid bacillus by this means gives results as reliable as those obtained in streptococcal or pneumococcal infections by the use of serological tests. It is thus possible to prove or disprove the connection between cases of typhoid fever occurring sporadically or during an outbreak, and between a carrier and the patients for whose infection the former is being held responsible.

PRACTICAL VALUE OF THE TYPING METHOD

Reports so far published from Canada, China, the United States of America, Great Britain and the Middle East amply corroborate the epidemiological significance of this observation. In Britain the new method has been employed extensively since 1940 by the organisation known as the Emergency Public Health Laboratory Service and their experiences have led to the conclusion that phage typing is an indispensable aid to successful epidemiological field-work (Felix, 1943).

A paper read before 70th meeting of the Seth G. S. Medical College Staff Society held on 8th November 1947 with Dr R. G. Dhayagude in the chair

VI AGGLUTINATION IN THE DIAGNOSIS OF TYPHOID FEVER
AND IN THE DETECTION OF CHRONIC TYPHOID CARRIERS

Serological diagnosis of typhoid fever is now being carried out all over the world by the application of Vi agglutination test (Bhatnagar, 1938 a) in preference to the time-honoured O and H types of agglutination, the interpretation of whose results is hedged with other faulty interpretations. The detection of the Vi antibody in the serum of a patient definitely means that typhoid infection is present. The only confusion that may arise is in cases where the patient is a chronic typhoid carrier, which can be easily excluded from clinical manifestations. The technique of Vi agglutination has been much simplified since the introduction of typhoid strain "Vi I" (Bhatnagar, Speechly and Singh, 1938) which is a pure reagent for the demonstration of typhoid Vi agglutinations. In Britain such standard agglutinable suspensions have been supplied to different Laboratories formerly by the Oxford Standard Laboratory (Medical Research Council) and now by Central Enteric Reference Laboratory in London.

The frequency of a positive Vi reaction in chronic typhoid carriers is remarkably high. Felix (1943) states, "from my experience over a period of nearly 10 years it would appear that not more than 5 to 10% of true chronic carriers will give a negative Vi reaction. When however, the carrier condition has lasted for a very long time, for example, periods of 30 or 40 or more years, the powers of producing Vi antibody often tends to be exhausted."

Arrangements are now being made to establish typhoid Vi Bacteriophage diagnosis Centres in different Provinces in India and specially in Bombay at the K E M Hospital under Professor Dhayagude who according to my knowledge is the only investigator in this country with experience of Vi phage problem.

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ANOMALIES OF THE SPINAL PART OF THE AXIAL SKELETON AND THE COSTAL CARTILAGES

by

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The various anomalies observed in the course of a study of 150 radiograms of normal individuals and 12 skeletons have been presented. The study was primarily undertaken to obtain the normal measurements of the spinal column in adult Indians. The subjects were mostly young students from the College and members of the staff. The average age of the whole series was 22.18 years. It included 100 males and 50 females.

The Embryology and Morphology of the spinal column was discussed in detail at the out-set. The congenital anomalies are attributed mainly to 4 causes —

- (1) Failure or arrest of development at some stage
- (2) Faulty development due to persistence of atavistic formations especially the costal elements
- (3) Cephalad migration of the pelvic girdle and nerve plexuses of the limbs, and
- (4) Miscellaneous factors such as race, habits and occupation

66.3% showed some type of anomaly. Changes in the numbers of the vertebra in the cervical and thoracic and lumbar segments were observed in 86.6% of cases. 8% had 23 presacral vertebra and 0.66% had 25 presacral vertebra. The changes in the body were represented by one case of hour-glass vertebra, one of fusion of two vertebra, one of synchondrosis and one of spondylolysis.

Spina bifida occulta was observed in 20.6% of the cases, the preponderance being in males. These figures vary considerably from those published by various authors. There were 15 cases with more than 12 pairs of ribs, 8 of lumbar ribs and 6 of cervical ribs. Two cases of styloid processes in the lumbar region were also found.

A total incidence of 6% of cases of cervical ribs was observed. These cases were further classified into four grades according to stage of development. There were 21 of grade 1, 18 of grade 2, 8 of grade 3 with well marked development and 1 of grade 4 with fully formed ribs.

The 12 skeletons studied were obtained by separate maceration of the cadavers to prevent mixing of bones. Out of the 12, there were 5 with normal vertebrae, 9 with 24 pre-sacral vertebrae and 3 with 23 presacral vertebrae.

Spina bifida occulta was found in 3. One instance each of lumbar and of the sacral segments, 11 pairs of ribs and one of cervical ribs were also found. The total number of skeletons studied was too small to compare with the larger series studied by means of radiography.

A paper read at the 77th meeting of the Seth G S Medical College Staff Society held on 18th December 1947 with Dr. R. P. Koppikar in the chair.

Critical Notes and Abstracts

HOME HYDROTHERAPY FOR MINOR REACTIONS DUE TO TENSION (James R. Gay, M.D., Fellow in Neurologic Surgery, Mayo Foundation) Symptoms of tension are part of a normal biologic response to the physical and emotional stresses of everyday life. When a reaction due to tension becomes exaggerated or prolonged, patients so afflicted may consult a physician for relief from the unpleasant physiologic concomitants. Most of the minor reactions of this type can be successfully managed by the physician regardless of his special medical or surgical interest.

The patient benefits from an evaluation of his physical status, general reassurance and a discussion of the obvious causes of his condition. However, the patient expects prompt relief from some of the symptoms which are responsible for his distress. Home hydrotherapy is a useful means of attacking disturbing sensations of tension, sensory and motor hyperactivity and mild visceral dysfunctions. It is safer and often more effective than prolonged sedation with derivatives of barbituric acid. The success of the method is dependent on the cooperation of the patient and the instructions of the physician in reference to certain essential details.

The patient is advised to obtain a bath thermometer in order to control the water temperature. The cost is about 50 cents. An ordinary bath tub is filled about three quarters full with warm water and the temperature of the water is adjusted to exactly 98° F (body temperature). In drafty bathrooms it may be necessary to drape an old sheet or blanket across the tub to prevent rapid cooling of the water after the patient is in the tub. The patient lies back in the tub so that only his head is above water. Drafts, distractions and disturbing thoughts should be avoided as much as possible during the time he is in the tub.

He should remain in the warm bath for a minimal period of twenty minutes. Warm water must be added at intervals of twenty minutes and the temperature of the water should be adjusted to 98° F every twenty minutes when the patient remains in the bath for long periods.

The usual reaction to the water at 98° F is a slight chill on entering the water. This is followed by diffuse cutaneous vasodilatation which produces a warm subjective sensation and a comfortable sense of fatigue. A maximal effect is attained if the patient becomes drowsy or falls asleep. If the patient must participate in activities following a warm bath, he is urged to follow the tub with a cold sponge bath or shower to dispel any sense of retardation. The cold sponge bath or shower is not advisable if the patient is retiring immediately. Hot or cold water has a stimulating effect and is unsuitable for patients suffering from symptoms of tension.

Warm tubs should be taken during that part of the day in which the distress from tension is maximal. These periods may occur any time day or night and should be carefully determined by the physician in order to instruct the patient to employ hydrotherapy at those special periods. Tubs taken before retiring may be useful in resolving difficulties in sleeping.

Home hydrotherapy, which has been described, is intended for the treatment of minor reactions owing to tension. In more severe condi-

tions the collaboration of a neuropsychiatrist will usually be required to evaluate the symptoms and their cause and to obtain recommendations for treatment

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Since the time of Hippocrates prolonged baths have been used for treatment of mental patients, and there is probably no first-class institution for the care of the emotionally disturbed in the country today which does not have an installation for hydrotherapy. Continuous tub baths and wet sheet packs are now standard procedures.

In addition to the fact that the type of bath described has a sedative and relaxing effect, which is efficacious in the treatment of overactivity and tension, the bath is a tangible procedure and something which the patient usually can do for himself, these facts in themselves are of therapeutic value. There is not much else, except the administration of sedatives, that the physician can do when called on to deal with a patient suffering from anxiety. One great advantage about this type of treatment is that it can be administered in the home without the necessity for special equipment. Care must be taken, of course, to prevent scalding, chilling or suicidal attempts if the patient is depressed. Unlike the use of large doses of barbiturates for tension and anxiety, the procedure outlined by Dr Gay can be used frequently without fear of unpleasant after effects.

THE CHEMOTHERAPY OF CHOLERA (Bhatnagar and Divekar, Brit M J 1 788 1948) The cholera vibrio is one of the few organisms which seemed completely to have escaped the chemotherapeutic net. The treatment of cholera remained symptomatic, and consisted largely in combating the intense dehydration of the tissues by hypertonic saline rather than in destroying the vibrios. Attempts had indeed been made to combine sulfaguanidine with hypertonic saline but without any conspicuous success. In view of the impotence of chemotherapy it is therefore not surprising that in many outbreaks, especially where skilled nursing was unavailable, the mortality rates remained high. Bhatnagar and his colleagues (1948) described a new chemotherapeutic approach to cholera. Full data at present available on the treatment of cholera by a new sulphonamide compound provisionally termed "6257" have been presented.

The starting-point for this investigation was an observation made by Bhatnagar in 1939 that hexamethylenetetramine in a 10 per cent solution in normal saline killed the cholera vibrio in less than half an hour, even when the organisms were in high concentration. Attempts to link hexamine and sulphanilamide produced compounds which gave promising results in the treatment of animals experimentally infected and in human cases of cholera. Meier and Druey (1946) of Ciba evolved a new product, "6257", by the condensation of two molecules of sulfathiazole and three molecules of formaldehyde. The exact constitution of the new compound is at present uncertain though its formula is given as $C_{21}H_{21}O_6N_6S_4$. If it is really a condensation product and not, as are most sulfonamide derivatives, a substitution in or an addition to, the radicals of sulfanilamide, it represents a type of compound the chemotherapeutic possibilities of which have not yet been fully explored.

Preliminary *in vitro* experiments showed that "6257" was bacteriostatic or bactericidal against the Inaba and Ogawa strains of *Vibrio cholerae*. Owing to the relative insolubility of the drug in water it had to be tested as a 20 per cent suspension in 2 per cent gum arabic in distilled water. In mice the therapeutic activity was tested against the Inaba strain, twice the minimal lethal dose of organisms being given intraperitoneally. The effectiveness of the drug was considerably greater when it was given by mouth. This is apparently due to the fact that it is very slowly absorbed after oral administration. Even when injected absorption into the blood stream is slow, but as excretion also is slow it is possible to maintain in the blood of mice an effective therapeutic level by an initial dose of 80 to 90 mg of the drug, followed by 40 mg a day for four days. Subcutaneous or intraperitoneal injection does not cause any irritation despite the formation of local depot.

Field trials were undertaken in the south-eastern part of the Madras Presidency during the November and December 1947. Records for the past seven years show that the infection is endemic in this area the maximum incidence, with a case mortality of about 60 per cent, being from September to February. The patients, who were mostly of the "untouchable" labouring classes, were treated in their homes without any nursing or general medical care. No additional treatment in the form of salines or other palliatives was given. All cases were diagnosed bacteriologically before beginning treatment and were then classified into three groups according to the severity of the disease and the length of time during which patients had been ill. In all, 85 patients were treated, and of these 82 survived. The average amounts given were 16 g for a child, 23 g for an adult female, and 25 to 80 g for an adult male. The subcutaneous route was first tried, but, contrary to what had been found in the mouse suffering from a cholera septicæmia, in man there was little or no therapeutic action. The drug was therefore given by mouth, with good results. To overcome the tendency to vomit, 0.5 g tablets were broken up and given in small amounts till the full dose of 6 g had been ingested in the course of two to three hours. If this practice did not succeed, the drug suspended in gum arabic, was given per rectum. The improvement, even in twenty-four hours, appears to have been remarkable, as purgation was reduced and nausea, vomiting, and cramps disappeared. Within forty-eight hours the temperature had risen to normal and dehydration was much less marked. As a rule patients could be said to have recovered at the end of seventy-two hours. Nevertheless, to ensure destruction of vibrios in the stools, a seven-day course of treatment was considered advisable. For adults the first day's dose was 10 g, the second day's 4 to 6 g, and thereafter 4, 2 and 1 g per day. No toxic results were noted even in the most severely ill patients a result which Bhatnagar and his colleagues suggest is due to the presence of the formaldehyde radical. It is remarkable that out of the whole series only three patients died, and they were in the group of those most seriously ill.

Though since the pathogenicity of cholera vibrio's is known to vary greatly in different epidemics it would be rash to assert that a panacea for cholera has been obtained, nevertheless the results achieved are so striking that they merit further investigation on the widest possible scale.

THE FUCHSIN TREATMENT OF CHOLERA—(A Castellani, Brit M J , 1 364, 1948) The fuchsin treatment of cholera consists in giving to the patient in the very first stage of the disease (in which as a rule diarrhea is present but vomiting is absent) basic fuchsin 0.2 g in cachet, soft gelatin capsule, or easily disintegrating pill, every fifteen minutes until a total of 1.6 to 2 g or more has been administered. Naturally with it should be associated all the usual general measures which have been found of benefit in the disease and especially saline plasma injections.

The rationale of the treatment is as follows. In Cholera, in the first stages, the vibrios do not invade the mucosa, but multiply in enormous numbers in the lumen of the intestine. If we possessed an antiseptic that could be given by mouth and was not injurious, it should be possible to attack, and devitalize or kill, a great number of the germs before their toxins are absorbed whether exotoxins which are apparently of little importance, or endotoxins liberated by the disintegration of the germs. Basic fuchsin is not a strong general antiseptic, but has a fairly powerful action on *Vibrio cholerae*. In recent investigation it was found that a watery solution of basic fuchsin, 1:1,000, would kill the cholera vibrio and that much weaker solutions had an evident bacteriostatic action. It was also found that basic fuchsin retains its bactericidal and bacteriostatic power on *V. cholerae* when dissolved in liquids, containing pepsin and other enzymes and in liquids containing proteins. The fuchsin, apparently devitalizes, and kills the organisms by staining and fixing them without delay disintegration taking place, and therefore endotoxins probably should not be able to be set free. The toxicity of basic fuchsin was found to be very low.

Castellani gave fuchsin to several patients with chronic colitis of varying origin, chiefly amebic and bacterial. The dosage was 1 to 2 g daily, divided into five to ten doses. No very striking improvement followed, but toxic symptoms were not noted. He gave it also to three normal individuals without any untoward effect. The urine became coloured red.

ANTICOAGULANT DRUGS (D J Hains-J Iowa State M Soc , 37,446, 1947) The main indications for anticoagulant drugs are in surgical patients, cardiac infarction due to thrombosis of the coronary artery and in thrombophlebitis. Two drugs are available, namely dicumarol and heparin.

Dicumarol is a white, tasteless crystalline powder. It is insoluble in water but is readily and quantitatively absorbed from the gastrointestinal tract. It is soluble in the organic solvents. *Dicumarol* does not act directly on the blood to prevent clotting. It does not prolong or prevent clotting in vitro. It acts on the liver to prevent the formation of prothrombin-B. In forty to forty-eight hours enough prothrombin-B is normally metabolized to cause a fall in the blood prothrombin and a prolongation of the clotting process. New prothrombin-B is not being synthesized, the old is metabolized with a net result of a drop in the blood prothrombin.

The platelets may be reduced and the clot may fail to retract. The drug increases the sedimentation rate. The NPN, blood sugar, WBC, RBC, bilirubin, calcium, fragility of RBC, icteric index, and platelets all stay within normal limits under *dicumarol* therapy.

There is no direct toxicity with the drug Nausea, urticaria, headache, general malaise and aching, especially in the costovertebral angles, occur in some patients

The administration of the drug is by mouth. It is usually given in a dose of 800 mg the first day and about 100 to 150 mg a day thereafter, depending upon the effect exerted. Some patients require very little and others more. Its effect is expected within forty-eight hours.

The prothrombin time determination is used to study the effect of the drug and to grade its dosage. It is the goal of dicumarol therapy to keep the prothrombin time between 27 and 60 seconds with 30 seconds as an arbitrary standard. This insures prothrombin levels below 50 per cent of normal. When the prothrombin time is 60 seconds, or less than 10 per cent of the normal prothrombin is present, bleeding occurs. Bleeding is classed as major or minor according to its severity which varies from occult blood in the urine to frank hemorrhage, both deep and superficial in type.

If bleeding appears, a large dose of vitamin-K is given. Sixty-four milligrams is recommended as the initial dose. The average ampoule of water-soluble vitamin-K for parenteral use contains only 1 mg. A large one contains five. The dose necessary to control hemorrhage is much larger. It may be necessary to give transfusions of whole blood as well. This raises the prothrombin level of a bleeding patient the most rapidly. Fresh blood should be used, for prothrombin-A disappears rapidly from stored-blood. Such blood, while by no means without anti-hemorrhagic value, is not as effective as fresh whole blood or plasma. Bleeding may continue for several hours after the administration of vitamin-K in large dosage and transfusions. This is frightening, but death from hemorrhage is not reported. The best safeguard is daily, careful watch over the prothrombin levels. Bleeding and unsuitable doses of vitamin-K are what gave dicumarol a dim reputation for a while. This is not justified now.

The contraindications to dicumarol are many, but they follow definite patterns. —(1) Dicumarol should not be used alone where it is necessary to prolong clotting before the end of forty-eight hours. This is the latent period of the drug. Where there is the need for an anticoagulant agent to act immediately, heparin is necessary. (2) The drug should not be used in patients who have jaundice or hepatic insufficiency, definite renal insufficiency, subacute bacterial endocarditis, blood dyscrasias with a tendency to bleed, recent operations on the brain or spinal cord, or in infants.

Dicumarol should be given cautiously to patients who have ulcerative colitis, open wounds or open bleeding lesions, vomiting due to gastric or intestinal obstructions, continuous or repeated gastric pain, patients in a poor state of nutrition, and parturient females.

Dicumarol is made from salicylic acid. In some people large doses of salicylates can produce the dicumarol effect of inhibition of prothrombin formation.

Postoperatively, dicumarol was used by the author in 1,000 consecutive patients. The initial dose is given before the operation. Postoperative thromboses and embolism were greatly reduced. The dosage is kept up about a week after the patient is ambulant.

In diseases of the coronary arteries with thrombosis and infarction, dicumarol has caused a great drop in thrombotic and

tations The advantages of dicumarol therapy in coronary thrombosis with cardiac infarction are (1) the prevention of extension of coronary thrombosis, (2) prevention of secondary myocardial infarction during the healing stage, (3) the prevention of the formation of mural thrombi, (4) prevention of phlebothrombosis during convalescence, (5) safety in digitalizing the heart after infarction

Thrombophlebitis involves a long disability Dicumarol reduces the length of illness by about two-thirds

Heparin is an extract of lungs, liver and intestines It is a strongly acidic compound of carbohydrate nature It directly stops clotting The probable action is that it prevents the conversion of prothrombin to thrombin Heparin also inhibits platelet agglutination

Given intravenously, heparin acts instantly Its action is not prolonged above two or three hours If it is to be used intravenously, it must be given continuously Given intramuscularly, its action is a little prolonged

Heparin may be given intramuscularly in a vehicle which allows only slow, and steady absorption Pitkin's solution is such a vehicle Heparin given this way begins to exert its effect within two hours, but the total effect is prolonged from thirty-six to forty-eight hours Pitkin's solution contains 100 mg of heparin

It may be used to give an immediate effect during the latent or lag period of dicumarol Its chief disadvantage is its expense Heparin does detoxify digitalis, ouabain and strophanthin It lessens anaphylactic shock in the guinea pig The contra-indications to the use of heparin are the same as those for dicumarol Its indications are likewise the same

ANTI-HISTAMINE DRUGS IN THE TREATMENT FOR TRIGEMINAL NEURALGIA.—Horton and Brennan present a case of typical trigeminal neuralgia treated by means of histamine desensitization The patient, a woman, had had facial pain for about 16 years During that period she had had several injections of alcohol and gas-screan neurectomy on the right side with no relief from pain Relief of pain on the left side resulted from a retrogasserean neurectomy on that side Upon entering the hospital in July 1947, the patient was given codeine sulfate hypodermically and later merperidine hydrochloride Neither of these drugs afforded relief from the intense pain During the next six days the patient was instructed to take 100 mg of "pyribenzamine hydrochloride" N N R (tripclennarmine hydrochloride) at the beginning of each attack of trigeminal neuralgia Relief of pain was complete upon taking this drug

In pain free periods typical attacks were provoked by the administration of histamine After repeated injections of histamine this drug could no longer provoke an attack of trigeminal pain She was discharged on the 32nd hospital day, completely free of pain with the instructions to take 100 mg of "pyribenzamine" each time an attack of trigeminal pain occurred The authors state that although definite proof is not available their observations in this case are consonant with the following theses (1) The attacks of trigeminal neuralgia, in this patient were brought about by the periodic release of some agent resembling histamine, if not histamine itself (2) The release of the agent was provoked by exposure to some precipitating agent to which the patient

was exposed seasonably (3) The antispasmodic and sedative effect of "pyribenzamine" and "benadryl" were not important in precluding the trigeminal pain, because both atropine and phenobarbital were ineffective, therefore "pyribenzamine" and "benadryl" exerted their therapeutic effect by antihistaminic activity (4) The ineffectiveness of a provocative dose of histamine, after a series of subcutaneous injections was given, was due to a process of desensitization

(Horton Charles F. George Washington University Hospital, Washington, D. C., and Brennan Andrew J. Journal A.M.A. 136: 870-872 March, 1948)

MEDICAL MANAGEMENT OF THYROTOXICOSIS

William S. Middleton presents a historical review of the treatment of thyrotoxicosis. The growth of knowledge of the physiology and chemistry of the thyroid gland, particularly the established interrelationships among the endocrine glands have tended to preclude the surgical method of attack. Since the discovery that iodine is essential for the formation of thyroxine, but that its use may under certain conditions inactivate the thyrotropic hormone, the element has been used successfully in the control of endemic goiter. Iodine has come to be used in the preparation for surgery, since its use has decreased to a negligible level thyroid crises and mortality from subtotal thyroidectomy. Fluorine has been considered, as having antidotal action against thyroxine, however, experimental evidence is that sodium fluoride did not reduce the basal metabolic rate nor counteract the pharmacologic action of thyroid in animals.

Results from the use of x-ray are inconclusive. Radioactive iodine is receiving wide attention as a possible therapy of thyrotoxicosis. In experimental animals administration of ^{131}I resulted in almost complete destruction of the thyroid parenchyma. Cautiously adjusted doses to three patients with hyperthyroidism induced clinical remissions without adverse symptoms in four to six weeks. Four and one-half months later two of these patients were entirely well. The third required another small dose of radioactive iodine. Time and extended experience will be required to fix the appropriate dosage of radioactive iodine. By reason of its longer half life ^{131}I (half life 8 days) is preferred to ^{130}I (half life 12.6 hours). The clinical use of thiouracil and other antithyroid drugs was begun in 1943. In a series of 72 hyperthyroid subjects, thiouracil therapy resulted in maintenance of normal basal metabolic level for more than four months by 30 patients and for more than six months by 16 patients. In another series of 100 patients with thyrotoxicosis thiouracil induced remissions in 87. Prior administration of iodine may or may not delay and impair the action of thiouracil, and both iodine and thiouracil have been administered where surgery is contemplated with good results.

Agranulocytosis is one of the most serious adverse manifestations of thiouracil. Propylthiouracil has been advocated as a drug of choice over thiouracil as a result of its attributed lesser danger of neutropenic reactions. However, several cases of agranulocytosis have been reported resulting from the use of propylthiouracil. The author states that eternal vigilance is the best protection against grave consequences from agranulocytosis. Periodic counts of the leukocytes and their distribution should be made throughout the first four months of thiouracil treatment. Recently ergothioneine, a normal constituent of the

blood, was submitted to experimental study and was found to produce an effect comparable to oral thiouracil

(Middleton, William S. University of Wisconsin Medical School, Wisconsin Journal Ind. State Medical Assoc 41 295 301 March, 1948)

DIAGNOSIS AND TREATMENT OF ACUTE VASCULAR OCCLUSIONS IN THE EXTREMITIES Nelson W Barker presents an outline of diagnosis and treatment of vascular occlusions, pointing out the differences in treatment of occlusion in veins and arteries. Acute arterial occlusions may be caused by arterial thrombosis in situ or by arterial embolism which is usually the result of a detachment of a portion of an intracardiac thrombus which has developed in a fibrillating left auricle or on the surface of a recent myocardial infarct. Sudden occlusion of the brachial or femoral artery usually produces severe diffuse pain in the extremity distal to the point of occlusion and the onset of the pain is usually sudden. The affected part is pale and cold, arterial pulsations are absent distal to the point of the occlusion. If the condition is untreated gangrene may develop gradually after twelve to twenty-four hours.

The author bases treatment on the following considerations:
 (1) The ischemia of the limb is produced in part by the organic arterial occlusion and in part by severe secondary arterial spasm below the point of occlusion.
 (2) When spasm relaxes, extensive secondary thrombosis may occur in the arterial tree below the point of occlusion because of ischemic damage to the arterial endothelium.
 (3) An original thrombus may slowly extend proximally and produce more and more ischemia.
 (4) The skin and tissues of an extremity which has suddenly become ischemic are easily injured by heat, cold, chafing or other minor trauma of the skin.

On the basis of these considerations, the following plan of treatment is recommended:
 (1) Do not elevate the extremity.
 (2) Do not apply extreme hot or cold applications or massage.
 (3) Place the patient in a warm room.
 (4) Put patient on a Sanders oscillating bed, maximal low-foot, minimal low-head position, or put the patient in a low Fowler's position.
 (5) Wrap extremity loosely in cotton batting.
 (6) Give papaverine hydrochloride $\frac{1}{2}$ gram intravenously and repeat the dose in two hours if necessary.
 (7) Give two ounces (60 cc) of whiskey every four hours for the first two or three days.
 (8) Give 50 mg of heparin intravenously every four hours.
 (9) Give 800 mg of dicumarol the first day, 200 mg the second day and every day thereafter that the concentration of prothrombin is more than 20 per cent of normal. Discontinue doses of heparin when the value for prothrombin drops to less than 80 per cent of normal.
 (10) If relaxation of arterial spasm is not indicated by definite lessening of the manifestations of ischemia in six hours, block the regional sympathetic ganglion with procaine hydrochloride.
 (11) If this procedure does not improve the circulation in three hours and the occlusion is due to embolism, do an embolectomy.

The author confines his remarks concerning acute occlusion to the veins to acute thrombophlebitis of the deep veins of the calf and the popliteal veins and acute thrombophlebitis of the iliofemoral veins. Thrombophlebitis in these two regions usually occurs as a complication of a surgical operation, the puerperium, severe injury, acute infectious

disease, heart disease, blood dyscrasia or carcinoma. The important reasons for early diagnosis of thrombophlebitis are first that it marks the patient as having a tendency to more venous thrombosis and therefore pulmonary embolism and, second, good treatment during the acute stage may reduce the subsequent development of disabling chronic venous insufficiency of the limb. Treatment of patients with acute thrombophlebitis at the Mayo Clinic consists essentially of keeping the patient in bed with the leg elevated for one to three weeks and the administration of anti-coagulants to all patients except cases of blood dyscrasias with bleeding tendencies, subacute bacterial endocarditis, recent operation on brain or spinal cord, and patients in purpuric states. Litigation of veins is considered a second best method of prevention of pulmonary embolism and may be advisable in cases in which use of anticoagulants is contraindicated.

(Barker Nelson W., Mayo Clinic Rochester Minnesota. *The Journal Lancet* 68: 104-106 March 1948.)

AN ANALYSIS OF 727 MENINGOCOCCI CASES Hoyne and Brown report their experience with 727 patients admitted to Municipal Contagious Disease Hospital from January 1943 to December 1946 with a diagnosis of meningococcic meningitis. Among the patients, ranging in age from seven weeks to 71 years there were 108 deaths, or a fatality rate of 14.8 per cent. Sixty-seven of the patients were moribund when admitted, and among these there was pathological or clinical evidence of the Waterhouse-Friderichsen syndrome in 20 instances. If all moribund patients are excluded, the fatality rate is 6.2 per cent. A large number of the patients had meningococcemia and nearly all showed evidence of meningitis, 62.8 per cent had petechiae, and 69.8 per cent of the petechial smears were positive for meningococci.

Among the 423 patients who had an intrathecal tap as a diagnostic measure, the spinal fluid smear or culture was positive for meningococci in 94 per cent. When the clinical diagnosis was confirmed by petechial smear or positive blood culture an intrathecal tap was not considered necessary, as a consequence, the entire group of 727 patients had an average of less (0.7) than one lumbar puncture, 41.8 per cent of the patients had no lumbar puncture after admission. There was but slight difference in therapeutic efficiency regardless of the sulfonamide drug that was administered. However, the actual percentage of recoveries was highest for the patients who were treated with sulfathiazole.

Fatality rates for the several drugs were as follows: Sulfadiazine 14 per cent, sulfathiazole 12.8 per cent, sulfamerazine 13.3 per cent, and sulfapyridine 25 per cent. The average number of days ill prior to admission was 3.1 and the average number of days on sulfonamide therapy was 8.3. In spite of a short period of hospitalization (average 11.5 days) there was not a single instance of a relapse or recurrence following release from isolation.

The authors felt that their results in the treatment of 727 patients with meningococcic infections are conclusive demonstration that intrathecal therapy is not necessary for meningitis. Furthermore, they state that frequent lumbar punctures for drainage are not required and that penicillin is not a valuable adjunct in the treatment of meningococcic infections but is an efficient aid in the management of eye complications. The authors question the emphasis customarily placed on the value of sulfonamide blood levels when

considering prognosis, since although sulfathiazole levels are low, there is no doubt in regard to this drug's usefulness for the treatment of meningococcal meningitis

(Hoyne Archibald L. Chicago Illinois and Brown, Powine Hayes Annals of Internal Medicine 28 248 250 February, 1948)

TETANUS INCIDENCE AND TREATMENT This is a discussion of the clinical study of 76 cases of tetanus in Roper Hospital from 1936-1946. The author brings out salient points concerning the incidence, factors influencing mortality and the relative effectiveness of various methods of therapy. Of the 76 cases, ten were infants with tetanus neonatorum, death occurring in all ten cases. Tetanus neonatorum was considered a fatal disease and did not figure in the further study of the series.

The mortality in this series was roughly inversely proportional to the length of the incubation period. The mortality in those patients with incubation period of ten days or less was 52 per cent, in those whose incubation period was more than ten days, 28.5 per cent. The incubation period was known in 50 cases. The highest mortality occurred in three, four, and five days, although there was no significant drop in mortality until after the eighth day of the disease.

A factor which influenced the prognosis was the length of time which elapsed between the onset of the first symptoms and the development of general spasms. In general, the development of general spasms in a short time after the first symptoms meant a severe, rapidly developing infection, and the mortality in these cases was correspondingly high. Those patients who developed general spasms within two days or less after onset of symptoms had a mortality of 68 per cent. Those whose general spasms developed after two days after onset of initial symptoms had a mortality of 25.8 per cent. Roughly, the length of the incubation period and the length of time from the onset of symptoms to the development of general spasm gives indication of the severity to be expected in any individual case.

In the administration of tetanus antitoxin to patients in this series it was concluded that 150,000 units of antitoxin should be given intramuscularly during the 60 hours following admission to the hospital, the intramuscular route being preferable to either intravenous or intrathecal routes. Various types of sedation were used to produce relaxation of muscles and terminate convulsions, the most satisfactory of which was found to be Na-amytal intramuscularly and intravenously, and the use of avertin (tribromethanol with amylene hydrate) by rectum. While proper surgical care was considered essential, surgical intervention was not indicated simply because the wound was the focus of dissemination of the tetanus toxin.

Penicillin was considered ineffective in the prevention or treatment of uncomplicated tetanus, but was used as a necessary adjunct for the prevention of pneumonia. The author concludes that since 16.6 per cent of the cases in this series in which 56.6 per cent proved fatal were seen by a physician upon injury, at which time no prophylaxis against tetanus was given, this finding should serve as a stimulus to all who practice medicine to avoid neglect of this important part of the treatment of traumatic injuries.

(Robertson Henry C. Jr. Charleston 15 South Carolina, The Journal of the South Carolina Medical Association 44 73 77 March 1948)

THROMBOCYTOPENIC PURPURA HEMORRHAGICA

Rittershofer differentiates purpuras into those with diminished blood platelets and those with normal platelet count. He believes that only the thrombocytopenic purpuras are primarily hemorrhagic diseases. It is probable that anatomic alterations of the smaller vessels often account for the ecchymotic lesions observed in the non-thrombocytopenic forms of purpura.

Thrombocytopenic purpura hemorrhagica is judged to compromise a group of closely related hemorrhagic diseases characterized by reduction in the number of circulating platelets, prolonged bleeding time, decrease in capillary resistance, and spontaneous frank bleeding from mucous membranes and bleeding into the skin causing petechiae and ecchymoses.

Thrombocytopenic purpura hemorrhagica has two constant characteristics. A reduction in the number of circulating platelets, and a pronounced bleeding tendency. The two main organs affected are the spleen and the bone marrow. One group of workers believes that the thrombocytopenia is brought about by a hyperactivity of the spleen in destroying platelets, and has suggested the name "thrombolytic purpura." In favour of this view is the benefit obtained by splenectomy. Occasional failures have been explained as due to the presence of accessory spleens. On the other hand the platelet count may remain low even though the bleeding tendency is abolished or greatly decreased. Thrombocytopenia can occur in the absence of the spleen.

The author says that in 1938, Torland and Lee reported that they had prepared from thrombocytopenic spleens, an extract which, when injected into rabbits, caused a reduction in the platelets and a great increase in the bleeding time. Extracts from control spleens failed to produce these results.

Davidson and Sanford described babies born of mothers with purpura hemorrhagica, who at birth or shortly after developed purpura and had a low platelet count. All these infants recovered, thus making it appear likely that a toxic factor from the maternal organism was responsible.

Frank has stressed the view that the cause of chronic thrombocytopenic purpura is in the bone marrow, a toxic depression of the platelet mechanism. This view is based on the observation that all factors which depress the bone marrow bring about a fall in platelets. Thus, agents such as benzol, Röntgen rays and radium, bacterial toxins, and neoplastic metastases all produce a reduction in platelets. The evidence against the bone marrow as a primary factor in the disease is based on the relatively normal microscopic appearance of the bone marrow.

Discussing the relation between the number of platelets and the bleeding tendency, the author points out that since a severe thrombocytopenia is almost invariably found in hemorrhagic purpura, one is apt to conclude that the bleeding is dependent on a deficiency of platelets. A study of purpuric cases shows, however, that some patients bleed at a platelet level of 60,000 or higher while others may show only mild purpura with 20,000 platelets or less. The author cites the opinions and observations of various investigators on the role played by the platelets and by histamine.

He thinks that the final diagnosis rests on laboratory findings, reduction in the platelet count, prolongation of the bleeding time

positive tourniquet test, absent clot retraction, a normal or only slightly prolonged coagulation time. Every diagnostic aid is necessary to accomplish differentiation of primary from secondary thrombocytopenic purpura. Acute leukemia and aplastic anemia may be confused with thrombocytopenic purpura. The appearance of myeloblasts or lymphoblasts suggest the possibility of a leukemia. Sternal bone marrow examination should leave no further doubt, for a striking increase in immature leukocytes will be found, if leukemia is present. In aplastic anemia very little if any regeneration of the blood elements occurs.

In secondary purpura hemorrhagica, infection plays an important role. Careful search for foci of infections, teeth, tonsils, sinuses, adenoids is an important part of the diagnostic effort. Metastases to the bone marrow cause a reduction in the platelets. Toxic agents such as benzol, arsphenamine, and allergic sensitivity may do the same, so a careful inquiry as to foods and drugs should be obtained.

For adults removal of the spleen is the only therapeutic procedure which has consistently given effective and usually permanent results. In children, however, splenectomy must be considered as a last resort. There is no justification for subjecting a patient to splenectomy before the three most common causes of secondary purpura, viz., blood dyscrasias, toxic agents, and allergy, are ruled out.

All foci of infection must be eliminated particularly in children, because of the frequent association of purpura and infection. The use of moccasin snake venom has received much attention, but the value of this treatment has stirred up conflicting reports.

According to Kato repeated transfusion of blood is the most effective treatment of acute hemorrhage in idiopathic purpura hemorrhagica. Transfusion just before splenectomy is now the almost universal surgical practice.

Vitamin C can only be effective in those instances of capillary bleeding where there is a vitamin C deficiency.

In further remarks about secondary thrombocytic purpura, the author says that in some instances of infection it appears that the bacterial toxin acts directly on the bone marrow thereby depressing the production of platelets. This is demonstrated in the virulent type of smallpox and diphtheria. The same explanation may hold for the moderate depression of the platelets seen in influenza during the first week of the disease. In the majority of instances, however, the development of an allergic-like condition seems the most plausible explanation. Purpura associated with the acute exanthemata, with subacute bacterial endocarditis, and Rocky Mountain spotted fever is frequently seen. Otitis media, tonsillitis, infected sinuses, and acute upper respiratory infections are often followed by a typical picture of purpura. Sometimes a long period of three weeks may intervene between the infection and the appearance of the purpura.

Certain drugs which have no direct action on the bone marrow can in certain sensitized individuals nevertheless cause a marked fall in the platelet count which is accompanied by a bleeding tendency. The list includes quinine, iodine, belladonna, and nevarsphenamine.

(Pittschofer C. R. Cincinnati, Ohio, *Ohio State Medical Journal* 44, 154-158 February 1948. The author is connected with the University of Michigan Medical School, Ann Arbor, Mich., Cincinnati General and Children's Hospital, University of Cincinnati.)

TYPES OF CIRRHOSIS OF LIVER RESPONSIVE TO TREATMENT Morrison says that in recent years several innovations in the treatment of cirrhosis of the liver have aroused interest. Various preparations such as choline, cystine, methionine, protein hydrolysates, liver extract, etc., have been offered in the hope that these will be effective. This paper attempts to clarify the conditions under which cirrhosis of the liver can be expected to improve or deteriorate.

For purposes of treatment, the author differentiates between cases of fatty and of nonfatty cirrhosis. He shows that cases of fatty cirrhosis of the liver are usually those of alcoholic etiology, in which fatty infiltration and/or fatty degeneration are prominent. Fatty cirrhosis of the liver appears to be a nutritional deficiency disease, particularly when alcoholism with an inadequate dietary is the etiologic agent.

The atrophic or advanced form of hepatic disease develops in from two to 20 years. In this form the liver is apt to be smaller in size than the normal liver with a nodular surface and thick capsule. Fat is usually absent, but small amount may still be present.

The author outlines a combined intensive treatment, which consists of a maximum protein (three meat servings, daily, plus skimmed milk), high carbohydrate, low fat diet, daily injections of 5 cc. of a "whole" liver extract, highly potent injections of Vitamin B-complex, daily oral Vitamin B-complex, and multiple "total" vitamin capsules together with 2 Gm. each of methionine and choline daily.

The author compares the results of this treatment on 20 patients (11 without ascites and nine with ascites) with the results obtained in 23 patients who were treated only by such methods as were in use in 1938, that is, by paracentesis, diuresis, high carbohydrate diet and palliative therapy; this group contained 11 cases without ascites and 12 with ascites, and was called the "untreated" group.

After two years, all patients in the treated group without ascites were alive, as compared with a 27 per cent mortality rate in the control series.

Sixty-two per cent of the treated patients without ascites had returned to normal activity in two years as compared to 18 per cent of the control group. Thirty-four per cent of the treated patients with ascites had returned to normal activity in two years as compared with 17 per cent of the control series.

When these results were broken down the author found that excellent therapeutic results occurred in those patients suffering from the alcoholic type of cirrhosis of the liver, i.e., the fatty or portal Laënnec cirrhosis in the early or moderately advanced states. In the terminal form of the atrophic portal cirrhosis cases, with a shrunken liver, the therapeutic response was frequently indifferent or a failure—a sharp contrast to the prompt improvement seen in the early or moderately advanced stages of this disease.

(Morrison, L. M., Los Angeles, Calif., *Review of Gastroenterology* 15: 110-132 February, 1948.)

Our Problems · a forum for discussion

THE FUTURE

"What time holds in store for the world is difficult to predict. The future is like a stage on which the props are all set and the lines rehearsed, but which is still hidden from the waiting audience. Who could have foreseen the shattering events which followed both before and after the Battle of Britain, in which the course of history was turned as certainly as it had been twelve hundred years before at the Battle of Tours, where it was decided whether Europe was to be Christian or Moslem? All that can be safely said is that the world has been shaken violently by a revolution in its politics, economics, communications, and weapons, which is forcing us to revise all the historic conceptions to which we have done homage for so many years. The only certainty is the present pattern of the world belongs to an outmoded design which is on its way out of history. With the inevitable reorganization of society, the opinions and conclusions as to the scope of the public health field are undergoing changes. There are as many perspectives as there are interests concerned, and one's opinion is almost always influenced by one's own particular interest and background.

"A glance into the crystal ball, and the magic word "freedom" flickers into sight. A few lines may not be amiss about this word, so beloved by politicians and propagandists alike. Freedom without qualifications is an abstract noun, whose meaning varies with each person's sense of value. In sober moments of meditation, everyone of us must surely realize that no one can be fully free. Some men and women prefer freedom from financial cares, others the freedom to pursue all branches of medical practice and art for the benefit of society. Strange that those who are often most voluble in crying aloud that they will never, never be slaves, usually endure without a murmur the slavery of a routine occupation. There is, however, one freedom that all of us desire—that, freedom from ill health for everybody. Man has always considered health as an inalienable right, while he resented disease as a misfortune. He does not appreciate the fact that health is a privilege which requires continuous efforts in order to be maintained.

—K. G. MEYER

PUBLIC HEALTH EDUCATION

"Whom should we educate and how shall we educate them? Certainly, the answer to the first question is, "Everyone." Health, not only as a right of citizenship but as a duty, can be made a suitable and arresting subject for lecturers and discussion groups. The role of diet and cooking, cleanliness and the use of leisure should have special emphasis. The periodic health examination must in time become accepted practice not only in infancy and childhood and for the person leaving high school, but it also must be made a statutory preliminary to student life, employment, and at intervals thereafter. The leaders of industry have still to learn that their most sensitive and indispensable machine is the human machine, and that the improvement of working conditions is both a human duty and an urgent economic necessity. The doctors and statisticians and welfare officers must be their teachers, the engineers and architects their associates.

"But how are we to devise an education for the legislator? Would it be too much to suggest that simple courses of instruction in vital

statistics, in the correlation of mortality with occupation and overcrowding, in the recreational, nutritional and environmental needs of the people, should be made available to those who later sit in city and county councils or on the boards of supervisors? The health officer speaking before these groups often tends to lay too much stress on the achievements and too little on what has yet to be done. Where are the statesmen who with Benjamin Disraeli would say "The health of the people is really the foundation upon which all their happiness and all their power of state depend?"

"In this connection, thoughts recently expressed by Dr Alan Gregg are eminently appropriate. He says "The wisest course for us as doctors is to inform and instruct the public, constantly and competently, for the education of the public is the one inexhaustible source of strength in promoting the public health. Is there any sense in doing so little as we are doing now to inform those in authority as to what they could have?—the art of the politician is described as the ability to convert private desires into public demand. It seems to me that the plain duty of a doctor as soon as he knows with absolute certainty what causes a disease is to convert private scientific knowledge into public information and to be ready to act on a public demand for action."

—K F MEYER

ISOLATION

"The problems facing American medical science today are quite different from those which were pressing in 1900. After a century of colonial dependence, the United States finally emerged as an independent centre of medical science. It need only be pointed out, in conclusion, that nationalistic enthusiasm should not make the mistake of confusing independence with isolation. After 1918 the number of Americans who sought post-graduate training abroad rapidly declined. Many seemed to feel that native training facilities were now completely adequate, or even viewed any desire for foreign study whatever as a confession of cultural inferiority. This trend, with its implied threat of a 'continental complacency' (a view expressed by Dr Alan Gregg of the Rockefeller Foundation), may actually be interpreted as a last vestige of colonialisms as an exaggerated assertion of independence rarely made in European societies. True scientific maturity implies rather the opportunity, now before this country, of exchanging students as well as knowledge freely with all other progressive lands."

—R H SHRYOCK

THE SCIENTIST AND THE SOCIETY

"The great threat of our age to human welfare, as I see it, is that Societies led or driven by industrialism are gathering the individual into their fold as a service unit. The individual as a member of Society thus must do a Society's bidding, regardless of the particular pattern that social organization might temporarily represent. To the true scientist, the present frame of social organization is not the end of all wisdom but just another phenomenon to be viewed objectively in the course of his inquiries. The scientists' limits are the boundaries of the universe, and his function cannot, without destroying him, be limited to the service of any particular social order. Industrial, social, religious, and political patterns are not yet drawn to serve mankind. It is to be

hoped that each governmental power will provide an oasis for students who are individual elements of mankind first and servants of society last. Otherwise, intellectual growth will wither and die. Medicine is dedicated to the service of man and not to a social order. In this relation, Medical Research in its broadest sense has a pre-eminent call upon every social structure for support not merely for immediate needs but for the discovery of broad principles upon which the health of mankind depends. Let each social order, therefore, give the scientist a free hand and provide him with the environment and the tools he needs, make him accessible to students, for he is essentially a teacher, make the university his home, and *otherwise, for humanity's sake, leave him alone*."

—GOODPASTURE

15 August 1948

WISHES

(WISHED ON SEEING THE CROWDS OF REVELERS ON THE EVE OF 15 AUGUST 1948 IN THE BEAUTIFUL CITY OF BLACKMARKETEERS, PROFITEERS, SELF SEEKERS, SCHEMERS, HYPOCRITES, USURPERS, AND CUT THROATS,—THE PRODUCT OF A HUNDRED AND FIFTY YEARS OF POLITICAL SERVILITY, INTELLECTUAL STERILITY AND MORAL BANKRUPTCY)

*"I wish I loved the Human Race,
I wish I loved its silly face,
I wish I liked the way it walks,
I wish I liked the way it talks,
And when I'm introduced to one,
I wish I thought WHAT JOLLY FUN!"*

(WALTER RELEIGH)

QUESTIONS

*"Will it be so again
That the brave, the gifted are lost from view,
And empty, scheming men
Are left in peace their lunatic age to renew?
Will it be so again?"*

*"Must it be always so
That the best are chosen to fall and sleep
Like seeds, and we too slow
In claiming the earth they quicken, and the old usurpers reap
What they could not sow?"*

*"Will it be so again—
The jungle code and the hypocrite gesture?
A poppy wreath for the slain
And a cut throat world for the living? that stale imposture
Played on us once again?"*

(CECIL DAY LEWIS)



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Original Contributions

INFANTILE PELLAGRA

REPORT ON FIVE CASES

by

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INTRODUCTION

It can no longer be doubted that classical adult pellagra occurs in India. Sporadic cases have been reported from several parts of the country and the literature reviewed by Raman (1940, 1948). An outbreak of pellagra was reported recently from a rural area of Bengal (Chaudhuri and Chakravarti 1947). But there are very few accounts of the disease among infants and children. Lately, considerable interest is developing round a similar condition reported from Tropical Africa under various names, viz, Kwashiorkor (Williams 1933, 1935, 1940) Infantile Pellagra (Trowell 1937, 1940, 1941) and Malignant Malnutrition (Trowell 1944, Trowell and Muwazi 1945). Similar cases were also reported from Mexico, Cuba, San Salvador and Costa Rica (Trowell 1940). In India, Carruthers' (1941) description of ten cases of pellagra from Bombay Province included for the first time one case, in a boy aged 7 years, of the infantile form closely resembling Trowell's Uganda cases. More elaborate account of four cases of Kwashiorkor among tea garden coolies of Assam was given by Hare (1947). Raman's series (1948) of 102 cases shows 4 of Infantile Pellagra.

The patients reported in this communication were from the local labouring class whose diet is known to be gravely deficient and among whom malnutrition is widely prevalent. A recent survey conducted in the Nilgiri Plantations (Ramalingaswami and Patwardhan, unpublished) revealed that their diet was deficient in calories and grossly so in calcium, vitamin A and thiamine. Our experience at the Clinic, during the past 10 months shows that deficiency diseases form about 15% of all the medical out door cases seen here. Of these, vitamin A deficiency, manifested as Bitot's spots and keratomalacia is the commonest malady occurring in children. Among adults, peripheral neuropathy including burning feet, hyporiboflavinosis and anaemias of both microcytic and macrocytic types are frequently encountered. Hookworm and round-worm infestations are very common. Malaria is rare.

The cases described below were seen by us at the Nutrition Clinic of the Nutrition Research Laboratories, Coonoor (South India), situated at an altitude of 6000 feet. They came under our observation during the months of April, May and June of this year although the Clinic was functioning from July last year.

It is regretted that complete investigations could not be carried out on these cases and unfortunately, in every case, post-mortem examination was refused. The purpose of the communication, however, is to point out the existence of the disease in this part of India in order to facilitate its recognition and thorough investigation.

CASE REPORTS

Case No 1 —

M M, female child, aged 1 year, case 128, admitted 12-4-48

History — Second child, born full term, teething started at 8th month, the first child aged 3½ years was under our observation for nutritional oedema at the same time. The earliest abnormality noted about 2 weeks ago was oedema of the hands and feet, followed by diarrhoea. Few days later, a peculiar dermatosis started with the appearance of dark areas on the flexures of the knee and elbow joints, which broke down and peeled off leaving pale areas. A change in the voice to a hissing monotonous note was noted 8 days before admission. The child was being breast-fed.

On Examination — Extremely irritable, ill developed child (Fig 1) with pitting oedema of hands and feet. The voice was thin and inaudible. The skin showed moist reddish white areas on both the upper and lower extremities surrounded by hyper-pigmented skin which was tending to crack and desquamate. The lesions were most marked over the popliteal and antecubital spaces, groin folds, vulva and the back (Fig 2). The skin of the face was pigmented except over the cheeks which were unusually pale. Liver was palpable one finger below the costal margin, spleen was not palpable, there were cheilosis and angular stomatitis, blepharospasm, matted eyelids, conjunctival hyperaemia and circum-corneal injection. Hair was dry and brittle but not discoloured. There were crepitations at both lung bases and the heart was not dilated.

Urine — No abnormality except a trace of albumin.

Faeces — Plenty of fat globules, otherwise nothing abnormal detected, on culture, no pathogenic organisms isolated.

Blood — R B C 2 40 mill/c mm, Hb 8 gm %, W B C 12,000/c mm.

Treatment — 12-4-48 Breast milk discontinued, intramuscular injections of 5 mgm of riboflavine, 5 mgm of thiamine hydrochloride, and 100 mgm of nicotinamide were given. Frequent feeds of cow's milk and marmite one tea-spoonful every four hours were administered.

13-4-48 General condition better, voice returning to normal, blepharospasm unproved, child taking interest in the surroundings. Same treatment continued.

14-4-48 Skin lesions showed drying and peeling effect. Same treatment continued.

15-4-48 Skin lesions completely dried up and desquamating. Same treatment continued.

16-6 48 Child looking dull and lethargic in the morning, gradually became comatose and died at 6-0 p m

Summary —The case presented oedema, pellagrous skin changes, hepatomegaly, steatorrhoea, anaemia and evidences of hyporiboflavinosis. The loss of voice and its return to normal after the administration of thiamine hydrochloride are suggestive of infantile beriberi. The picture resembled that of pellagroid-beriberi described by Castellanos (1935) among young children of Cuba. Death occurred after a period of betterment and was sudden and unexpected.

Case No II —

T S, female child, aged 6 months, Case 132, admitted 20-4 48

History —First child, was being breast-fed, no other food was given. The illness started about a week before with diarrhoea and the appearance of pale and pigmented areas on the skin. The skin changes appeared first on the back of the thighs and spread upwards to the buttocks and downwards on to the popliteal space. They were black to start with and later peeled off leaving white areas in their wake. Similar changes commenced on the flexor aspect of the elbow joints. Numerous stools containing blood and mucus were being passed every day for four days previous to admission.

On Examination —Highly irritable child, with pitting oedema of both the legs, intense blepharospasm, and rigidity of the neck. Hair on the scalp was dry but not discoloured. There were areas of alopecia. The entire skin of the lower limbs and buttocks showed pale white areas surrounded by dark hyperpigmented skin. The border between healthy and affected zones was not clear-cut. Severe lesions were present over the gluteal region, the groins and vulva. Slight depigmentation of the skin of the antecubital space was to be seen. Liver was palpable three fingers below the costal margin with a soft edge, spleen was not palpable. Conjunctival hyperaemia and circumcorneal injection were present in both eyes.

Urine —Nil abnormal

Faeces —Blood and mucus present, no *Entamoeba histolytica*, trophozoite or cystic forms, no helminthic ova. Culture no pathogens isolated.

Blood —R B C 4 07 mill/c mm, Hb 5 3 gm %, 38,500/c mm

Treatment —20-4-48 Intramuscular injections of 100 mgm of nicotinamide, 5 mgm each of riboflavin and thiamine hydrochloride. Marmite, shark liver oil and milk feeds by mouth.

21-4-48 General condition appeared better, skin lesions seemed to dry up, diarrhoea not improved, blepharospasm lessened. Same treatment continued.

22-4-48 Child died at home. As the child was not hospitalised, immediate condition before death is unknown.

Summary —Diarrhoea, oedema, dermatosis, hepatomegaly and anaemia were the main features of this case. There was alopecia without any depigmentation of the hair. She made an apparent recovery for a day and died the next day.

Case No III

D N, female child, aged 1½ years, Case 136, admitted 26-4-48

History —First child, was being breast-fed, no other food was given. Presenting complaints were diarrhoea, dermatosis and oedema.

Changes in the skin and diarrhoea started simultaneously a week before, followed by swelling of the hands and legs within two days. The skin changes started on the lateral aspects of the legs and thighs, and desquamated leaving pale areas here and there. The child was being treated outside with bismuth and kaolin for 3 days past.

On examination —She was an irritable child with pitting oedema of the legs, angular stomatitis, and lustreless dry thin hair on the scalp which showed brownish discolouration (Fig 3). The liver was palpable two fingers below the costal margin, with soft edge. The spleen was not palpable. The skin over the popliteal fossae, the groins, vulva and the antecubital fossae showed the characteristic changes (Fig 4).

Urine —Albumin trace

Faeces Fat globules++ Culture no pathogens

Blood R B C 3 54 mill/cmm, Hb 9.8 gm%, W B C 4,600/cmm

Treatment —26-4-48 Same treatment as for Case II

27-4-48 Child's condition unchanged Same treatment continued

28-4-48 Child died

Summary Fatty diarrhoea, oedema, dermatosis, hepatomegaly anaemia, discoloured hair, and clinical signs of riboflavine deficiency were the main features

Case No IV

J B, female child, aged 1½ years, Case 156, admitted 31-5-48

History First child, still being breast-fed, occasionally rice congee (gruel) was being given. Presenting complaint was swelling of the body. Duration of the illness was 15 days and started as diarrhoea followed by oedema.

On examination —Generalised oedema all over the body was present (Fig 5). Nephritis was eliminated on urine examination. No skin changes could be detected at that time. The child was put on a high protein diet consisting of milk, eggs and marmite. For a week there was no change in the condition of the child. Then small dark areas appeared on the skin of the popliteal, axillary and antecubital fossae. These began to break and exfoliate leaving pale white areas (Fig 6 & 7). The same process occurred on the inner aspect of the thighs, groins and vulva. The anterior abdominal wall revealed crazy-pavement-like dermatosis. The liver was palpable two fingers breadth below the rib margin with soft edge. The spleen was not palpable. Hair was dry and lustreless, but not depigmented.

Urine Albumin trace

Faeces Fat globules++ Culture No pathogens

Blood R B C 2 32 Mill/cmm, Hb 7 Gm %, W B C 6,500/c mm

Treatment —On the same lines as for cases II & III from 10-6-48. Child's condition showed no improvement, the skin changes progressed to involve surrounding areas. Child died on 25-6-48.

Summary —This case is very interesting as the child, while under treatment for nutritional oedema, developed skin changes of the pellagrous type and died.

Case No V

P M, female child, aged 3 years, Case 163, admitted on 1-6-48. The presenting complaints were diarrhoea, oedema, and colour changes

PLATE I



Fig 1 General appearance of Case No I showing oedema angular stomatitis, blepharospasm and dermatosis

Fig 2 Same child as in Fig 1 The pale depigmented areas surrounded by dark skin around knee joint are well seen

Fig 3 General appearance of Case No III Note dry pale discoloured hair angular stomatitis and dermatosis on flexures and vulva

Fig 4 Same child as in Fig 3, showing the alternating pale and dark areas on flexor aspect of the knee joint

PLATE II



Fig 5 General appearance of Case No IV before the development of skin changes Note massive oedema and pallor

Fig 6 and Fig 7 Same child as in Fig 5, 10 days later showing typical depigmented patches on flexures, thighs and vulva Skin of the abdominal wall shows a crazy pavement appearance.

in the skin. No adequate history was available as the child was brought by some distant relations who did not know the antecedents of the case. The child was brought in a moribund, comatose state. The skin of the popliteal and antecubital areas showed the typical depigmented patches surrounded by dark cracked skin. The skin of the groins and vulva was also implicated. The hair was dark, dry and brittle. The liver was just palpable. The child died within a few hours of admission.

Urine not available

Faeces Watery, microscopic examination revealed no abnormality

Blood R B C 2 53 mill/cmm, Hb 9.7 gm %, WBC 6,800/cmm PCV 80 c c %, MCV 118.5 Cu, MCHC 82.8%

Summary Diarrhoea, oedema, enlargement of the liver, pellagrous skin changes, and macrocytic anaemia terminating in a comatose state followed by death were the main features of the case.

DISCUSSION

The cases described above show a uniform characteristic picture. Their ages varied from 6 months to 3 years. The diets consumed by their parents were markedly deficient in total calories and essential nutrients. The onset was sudden and the course rapid and fatal. They all had oedema, diarrhoea, enlargement of the liver, anaemia and pigmentary changes of the skin resembling pellagra. Four out of the five cases showed fatty stools and hyporiboflavinosis. Case V wherein sufficient blood could be collected for determining the haematocrit value, revealed that the anaemia was macrocytic. Thus, the picture closely resembles the syndrome of Malignant Malnutrition (Trowell & Muwazi 1945), also known as Kwashiorkor (Williams 1938) and Infantile Pellagra (Trowell 1937). The only difference seems to be lack of depigmentary changes in the hair of the cases reported above. Brownish discolouration of the hair was present in one out of the five cases. The question, however, arises whether red hair is essential for a diagnosis of malignant malnutrition. Williams himself (1940), who was the first to describe adequately the condition on the Gold Coast does not regard it as specific. Hughes (1946) describing 65 cases from the African Hospital, Lagos, states "We see depigmentation of the hair in some cases of Kwashiorkor, but alopecia rather than achromotrichia is the distinctive lesion". Trowell regards the name Kwashiorkor unsatisfactory as the red hair is not evident in adult cases and observes "this redness is probably peculiar to the dark skin of the African, this may explain why the syndrome has seldom been seen in Asia" (Trowell & Muwazi 1945).

NOMENCLATURE AND AETIOLOGY

There is a bewildering number of names given to the condition as observed in different countries and in different parts of the same country. This is as it should be until its aetiology is better known. This brings us to a discussion of its relation to the recognised states of malnutrition, especially pellagra. It is a disease of the poor and under-fed. The symmetrical exfoliative hypopigmented lesions on the skin resemble pellagrous dermatosis, even though their distribution is not in the adult fashion. Areas exposed to friction and pressure are the sites of election, and this is regarded by Stannus (1934, 1936 & 1944)

as characteristic of pellagra Flexures of the elbows and knees, the buttocks, groins and vulva are commonly affected The partial response of the skin lesions to nicotinamide administration is also suggestive But the condition, unlike adult pellagra, is sudden in its onset, rapidly fatal and is not relieved by vitamin therapy, including nicotinamide

Hughes (1946) suggested that a causal relation exists between Kwashiorkor and riboflavin deficiency But riboflavin deficiency is not invariable in Kwashiorkor Four out of our five cases showed clinical evidences of hyporiboflavinosis but the results of administration of 5 mgm of riboflavin intramuscularly every day were disappointing

What is the relation of this syndrome to Nutritional Oedema? The oedema, which is so constant a feature of the disease was shown to be associated with hypo-albuminaemia (Trowell & Muwazi 1945) Case No IV which was under our observation for nutritional oedema developed the typical skin changes in the course of one week The deficiency bowel pattern said to be present in this condition (Brown & Trowell 1944) was observed in protein depleted animals (Barden et al 1938)

Despite all this association of the disease with the recognised states of malnutrition, it is resistant to the usual forms of nutritive therapy Vitamin therapy and protein supplementation have been singularly disappointing in our cases Gillman and Gillman (1944, 1945 & 1946) and Trowell (1946) obtained excellent results on the administration of dried stomach, although Gelfand (1946) was unable to confirm this finding in his South Rhodesian cases The Gillmans regard fatty infiltration of the liver as the essential pathological lesion in Kwashiorkor They found that there was no rise in the plasma protein values on administering protein hydrolysates as a result of this hepatic damage Holmes and Trowell (1948), by chemical analysis of liver biopsy specimens of cases of Malignant Malnutrition have shown that there is a functional failure of the liver cells to store glycogen when presented with abundant amounts of glucose Recent work of Davies (1948), however, proves that changes in the pancreas are primary and more constant than those in the liver The steatorrhoea observed in our cases and elsewhere may be related to pancreatic dysfunction Trowell and Muwazi (1945) were of the opinion that steatorrhea and the presence of undigested protein and starch in the faeces of their patients could not have been due to rapid passage of food through the gastrointestinal tract, but that it was probably due to the failure of appropriate enzymes to act on these substances The later work of Davies (loc cit) tends to lend support to this suggestion, It will be worthwhile to investigate, therefore, the nature of pancreatic involvement in cases of infantile pellagra

SUMMARY

- 1 Five cases of pellagra occurring in infants between the ages of 6 months and 3 years are described
- 2 The condition is sudden in onset and attended by high mortality
- 3 Vitamin therapy and protein supplementation were totally disappointing in results
- 4 The clinical picture closely resembles the syndrome occurring in Tropical Africa, variously designated Kwashiorkor, Infantile Pellagra

and Malignant Malnutrition The aetiology of the condition is discussed

The authors are indebted to the Director, Nutrition Research Laboratories for his helpful suggestions at various stages, and to Messrs. Hoffmann La Roche for the free supply of vitamins used in these cases

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ONSET-SYMPTOMS OF PAINLESS MYOCARDIAL INFARCTION

by

LAURENCE E HINES, and JAMES JORDAN HINES

The sudden onset of severe substernal or epigastric pain and dyspnoea, associated with symptoms of shock, and followed by fever and leukocytosis is a commonplace and well known picture of coronary occlusion with myocardial infarction. The majority of patients with the disease fit into a pattern such as this, but genuine difficulty in making the diagnosis may occur when the symptoms are atypical and particularly if pain is absent. The electrocardiograph tracing does not always supply the answer. Many patients may reach the necropsy table before the diagnosis is made. This study is an attempt to analyze the diagnostic failures and to evaluate critically the onset symptoms.

Prior to Herrick's studies the disease was thought to be a fatal one. Herrick pointed out (Table I) that there were patients with mild manifestations and patients who recovered in spite of severe symptoms.

TABLE I

Herrick's Classification of Coronary Occlusion

Instantaneous death, no death struggle
Death within a few minutes or hours
May be found dead or in death agony
Severe cases, death delayed for hours or
days or months, may recover
Cases with mild symptoms, often due to
occlusion of small arteries

Many factors influence the onset symptoms and failure to evaluate them often is responsible for a mistaken diagnosis. In Table II some

TABLE II

Factors Influencing Symptoms

Size of infarction
Location of infarction
Rapidity of development of infarction
Adequacy of coronary artery anastomosis
Pre-existing damage to myocardium
Individual or constitutional sensitiveness of patient
Variation in pathways for transmission of pain impulse
Severity of pain barrage

of the factors are listed. The gravity of the symptoms generally are proportional to the size of the infarct. Tiny infarcts may produce very mild reactions or the incident may be symptomless. Proof for

this is shown by the frequent autopsy findings of multiple scars of small healed infarcts in the myocardium. Great variation in symptomatology is produced by the varying *location* of infarcts. If the infarct involves only that portion of the wall near the endocardium the likelihood of pain is less than if it is close to the pericardium. Infarction of the septum may initiate abnormalities in the conduction system. If both sides of the septum are involved and if there is mural infarction, emboli may be carried both to peripheral and pulmonary end vessels.

An infarct which develops rapidly is capable of causing an unusual onset. It may cause sudden death, abrupt left ventricular failure or profound septic manifestations. In the old patient who has arteriosclerosis, compensatory collateral circulation has usually developed. This is a factor in lessening the initial shock of an occlusion and in diminishing the size of the infarction.

Individual or constitutional sensitiveness also is a cause of great variation in the intensity of onset symptoms. A constitutional factor by itself can account for a painless onset in one or intense anguish in another. The development of symptoms in all diseases shows similar constitutional variation.

One of the most important causes of atypical symptoms from coronary thrombosis is the anatomic variation of nerve pathways. Unusual locations of pain can be accounted for logically by knowledge of the course of the pain fibres after they leave the cardiac plexus. They enter the upper five or six thoracic sympathetic ganglia through which they pass without interruption and then on through *rami communicantes* to the corresponding spinal or dorsal root ganglia. Afferent pain neurons also pass through inferior, middle and superior cardiac nerves, through cervical sympathetic ganglia and over *rami communicantes* to cervical sympathetic ganglia, and over *rami communicantes* to cervical spinal ganglia. A few pain neurons are conveyed from superior cervical ganglia to trigeminal-ganglia. The majority of pain fibres from the heart course through the inferior cervical sympathetic and upper two or three thoracic ganglia. Therefore, the bulk of pain impulses reaching the upper dorsal ganglia are projected as pain in one or both breast regions. Pain along the inner aspects of arms is produced through brachial plexus connections. Neck pain is produced by pain impulses moving into cervical roots. Jaw pain is produced rarely, when the pain impulses reach the trigeminal nerve ganglion. Reference of cardiac pain impulses to lower levels of the cord not usually affected is in the probable explanation of pain in the upper abdomen.

In the study of a patient with suspected coronary occlusion we should keep in mind that the symptoms may be caused by pathologic changes or abnormal physiologic states (Table III). Thus a variety of symptoms are produced from the changes within the coronary vessel such as thrombosis or arteriosclerotic narrowing. The typical pain of the occlusion itself is of course well known, but often we find great trouble in differentiating uncomplicated angina pectoris from the pain of occlusion. To further complicate the picture angina pectoris without myocardial infarction precedes infarction in about one half the cases.

TABLE III

Onset Symptoms May be Produced by

| |
|----------------------------------|
| Occlusion itself |
| Muscle infarction |
| Embolie phenomena |
| Myocardial insufficiency |
| Involvement of conduction system |
| Reflex |
| Gastro-intestinal, diarrhoea |
| Vasomotor |
| Central nervous system |

Pain of unusual location and unusual reference has already been described. Mistakes in this category are numerous. Erroneous diagnoses comprise a long list. Pulmonary embolism is one of the most difficult diseases to differentiate, this is particularly true because electrocardiographic changes produced by pulmonary embolism are similar to those of coronary occlusion. Changes in the electrocardiogram are produced by hiatus hernia and this is often a very difficult differential problem. Other diseases, sometimes diagnosed erroneously as coronary thrombosis because of similarity in pain, are pleuritis, myositis of muscles of the chest, root pains from diseases of the thoracic spine, scalenus anticus syndrome, herpes zoster, aortitis, aortic aneurysm, mediastinitis, pericarditis, neoplasms, substernal aches of hypertension, valvular disease, fatigue neuroses and toxic states, flatulence with oesophageal spasms, oesophageal ulcer, and gall bladder disease.

TABLE IV

| Symptoms from the Occlusion |
|----------------------------------|
| Pain |
| Typical |
| Post-anginal |
| Unusual locations and references |
| Painless |
| Shock |

TABLE V

| Symptoms from Myocardial Insufficiency |
|--|
| Dyspnoea |
| Cardiac asthma |
| Acute pulmonary edema |
| Cheyne Stokes respiration |
| Cyanosis |
| Edema |
| Enlarged liver |

TABLE VI

| Symptoms from the Muscle Infarction |
|-------------------------------------|
| Chill |
| Fever |
| Leukocytosis |
| Heart rupture |
| Pericardial friction |

TABLE VII

| Symptoms from Involvement of Conduction System |
|--|
| Palpitation from paroxysmal tachycardia, auricular fibrillation, ventricular tachycardia, heart block, and extrasystoles |
| Cerebral symptoms from heart block |

Shock may be the only manifestation of the initial occlusion. More commonly it follows or accompanies pain. Sudden development of the symptoms or signs of myocardial insufficiency (dyspnoea, cardiac

asthma, signs of acute pulmonary edema, Cheyne-Stokes breathing, cyanosis, peripheral edema and enlarged liver) in a patient who has no valvular disease suggests the possibility of painless myocardial infarction. Shock may be associated with this picture. Arterial hypertension alone can be the etiologic agent of acute heart failure but also may be combined with myocardial infarction.

Fever and leukocytosis, symptoms of the necrotic infarcted muscle, are important from the diagnostic standpoint. Usually they are less spectacular than the other symptoms. Rarely they are the prominent symptoms of onset and then must be differentiated from other causes of fever especially intrathoracic diseases like pneumonitis or pleuritis. Rupture of the heart producing tamponade and sudden death is a rare mode of onset of myocardial infarction.

TABLE VIII

Symptoms from Embolic Phenomena.

Occlusion of peripheral vessels
Pulmonary infarction
Cerebral symptoms
Kidney and spleen infarction

When the occluded vessel produces initial changes in the septum or some important part of the conduction system, the onset may be characterized by symptoms of an arrhythmia. Frequently we see coronary occlusion ushered in painlessly with severe palpitation from paroxysmal tachycardia, auricular fibrillation, multiple ectopic beats, or ventricular tachycardia. Complete A-V dissociation with cerebral symptoms of heart block is encountered occasionally as the beginning symptom. Some of the most confusing modes of onset are those which are ushered in by symptoms and signs of embolic occlusion in distant organs. Unexplained gagrene of a portion of an extremity, sudden hemiplegia, sudden mesenteric artery occlusion, kidney colic, pain in the region of the spleen, hemoptysis, and pleural pain may be the initial symptom of the disease.

TABLE IX

| Reflex Symptoms |
|--|
| Gastro intestinal Nausea, vomiting, distension, "gas" eructation, diarrhoea |
| Central nervous system |
| Convulsions |
| Syncope |
| Dizziness |
| Vasomotor |

TABLE X

| Pain | |
|-----------------|-----|
| Chest pain | 54% |
| Substernal | 29% |
| Precordial | 25% |
| Arm pain | 24% |
| Epigastrium | 6% |
| Neck pain | 6% |
| Jaw pain | 2% |
| Absence of pain | 8% |

Reflex manifestations at the onset are common. As previously stated, wide variations are due to the anatomic peculiarities in the nerve pathways. Fortunately the great frequency of the reflex digestive

manifestations is now well known. In earlier days patients with the disease were tagged as having "acute indigestion." The Bureau of Vital Statistics even accepted this diagnosis as a cause of sudden death. Great increase in intestinal peristaltic action with diarrhoea is a common effect of the disease. Evidence of this effect may be seen in the agonal defecation observed in patients who have died suddenly.

Reflex manifestations in other regions are also observed. Thus we see convulsions, fainting, dizziness, and profuse sweating. The painless onset is the principal cause of diagnostic errors.

SUMMARY

Painless development of coronary occlusion and myocardial infarction is relatively uncommon. Lack of pain is a common cause of diagnostic failure. Other causes are failure to evaluate all factors which influence the symptoms. The factors which should be kept in mind are the size, location, and rapidity of development of the infarction, adequacy of coronary artery anastomosis, pre-existing damage to the myocardium, individual or constitutional sensitiveness of the patient, and, variation in pathways for transmission of pain impulses. Greater success in accurate diagnosis will be obtained by an understanding of the pathologic physiology of the disease.

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NEWER ANTIHISTAMINIC DRUGS

by

SIDNEY FRIEDLAENDER and ALEX S. FRIEDLAENDER

The introduction of antihistamine agents in recent years represents a significant advance in the symptomatic treatment of allergic manifestations. Widespread interest in this group of compounds has stimulated a search for new drugs which may perhaps exhibit greater clinical activity and less undesirable side action than those presently available. During the past year a number of new compounds, the majority closely related in chemical structure to those now in use, have been distributed for clinical trial in this country. Several of these show considerable merit, and are rapidly being introduced for general clinical use. In the ensuing discussion, the most promising of the newer drugs, Neoantergan, Neohetramine, Antstine, Thenylene or Histadyl, Tagathen and Thephorin, will be discussed. The indications and limitations of antihistaminic therapy in general, will also be reviewed.

EXPERIMENTAL BACKGROUND

It might be well at this point to review briefly the background of the participation of histamine in the allergic reaction, and the significant steps in the development of anti-histamine compounds. The evidence that histamine plays an important role in allergy has been largely indirect and based to a great extent on the resemblance between the anaphylactic state in animals and allergic symptoms in man. Histamine release during anaphylaxis in certain species of animal has been rather conclusively demonstrated. It has been shown that histamine is a natural constituent of living tissue, and that during anaphylaxis the histamine content of the shock tissue diminishes with a simultaneous increase in the circulating blood histamine which is sufficient to account for the vascular effects observed. Further the manifestations of histamine shock in certain species closely resemble those of anaphylaxis. Even the strongest proponents of the histamine theory, however, point out that histamine is only one of many substances released during anaphylaxis and in itself cannot account for all the manifestations observed. There is evidence that heparin, acetylcholine and potassium among other substances are released during this reaction in addition to histamine.

Direct evidence attesting to the role of histamine in the allergic reaction is relatively small and far less conclusive than in the case of anaphylaxis. Nevertheless sufficient conviction regarding this relationship has existed in the minds of certain workers to stimulate an investigation of the antihistamine activity of various chemical compounds. In 1937, Staub and Bovet working in the laboratories of the Pasteur Institute found that thymoxyethyldiethylamine (929F) was an antagonist of both the histamine and the anaphylactic reactions. Further study revealed another compound, N-phenyl-N-ethyl-N-diethylethylenediamine (1571F) to be even more active in these respects. In 1942, 2 other compounds, N-phenyl-N-ethyl-N-benzyl-N-dimethylethylenediamine (2325RP), and N-phenyl-N-dimethylethylenediamine

(2339RP) were investigated, and the latter was introduced for clinical trial in France under the trade name of "Antergan." In North America interest has centred around 2 other compounds, Benadryl and Pyribenzamine. One, a benzhydryl alkamine ether was described by Loew and co-workers and the other, a derivative of Antergan, was reported by Mayer et al.

PHARMACOLOGY

The majority of the new drugs shortly to be discussed have some chemical relationship to these earlier compounds. All have certain pharmacologic actions in common, the most important of which is an antagonism of all the major effects of histamine excepting its gastric secretory activity. In addition, all exhibit strong local anesthetic action, several times that of procaine. They differ greatly in other respects, some showing an atropine-like action, while others exert a spasmogenic effect in moderate or high doses. Certain drugs augment the pressor effect of epinephrine, while others block or even reverse it. It would appear, therefore, that the ability of these agents to influence allergic symptoms is based on their ability specifically to antagonize the pharmacologic effects of histamine. Early in the investigation of these drugs it was thought that the degree of histamine antagonism exhibited in the experimental animal might be an index of clinical activity. Wide differences in antihistaminic action, however, have not been apparent in the antiallergic action of these drugs. The relationships between antianaphylactic activity and clinical efficacy is perhaps somewhat closer. In our own experiments we have found less marked differences in these drugs against anaphylaxis, which is more nearly the case in their clinical action. At present there is no absolute proof of the manner in which these drugs exert their effect. The current belief is that they compete with histamine for the same receptor cell, displacing histamine from its point of action.

CLINICAL USE

Despite differences in chemical structure and in antihistaminic and antianaphylactic activity, all of the drugs under discussion are effective in varying degree against the same manifestation of allergy and relatively ineffective against others. Indications for use and clinical results obtained for the entire group may be briefly summarized as follows:

DOSAGE The average adult dose varies from 25 to 100 mg. Children tolerate doses of 10 to 50 mg. very well. For continuous symptoms, the drugs are recommended in 3 or 4 doses daily, preferably after meals and at bedtime. For intermittent difficulty they should be employed only as required. The effect of a single dose administered orally is usually evident within 30 minutes and is of several hours' duration. There is no evidence of lasting benefit from their use. The drugs are useful in the following conditions:

ALLERGIC SKIN REACTIONS OF THE WHEALING TYPE These include acute and chronic urticaria and angioneurotic edema, dermographism, and "serum sickness type" reactions following penicillin, sulfonamides, horse serum and other biologicals. The antihistaminics have their greatest field of usefulness in this group of conditions, benefiting from 50 to 80 per cent of cases.

PRURITIC SKIN CONDITIONS Relief of itching has been observed in 40 to 60 per cent of cases of atopic and contact dermatitis. Some cases of pruritis vulvae and ani are markedly relieved by the drugs.

SEASONAL HAY FEVER Relief of rhinorrhea and sneezing occurs in 50 to 80 per cent of cases. Some investigators report an even higher incidence of benefit. In our experience, relief of symptoms is seldom complete, though marked improvement is frequently evident. Patients receiving some desensitization therapy to the specific pollen allergen obtain greater benefit from these drugs than do those who are totally unprotected. In general, mild symptoms are more frequently benefited than severe ones. Observations in relation to the prevalence of atmospheric pollen indicate that the symptomatic effect of these agents diminishes as the pollen content of the air increases.

NON-SEASONAL ALLERGIC RHINITIS Benefit is evident in from 40 to 65 per cent of patients. The symptoms of rhinorrhea and sneezing are more frequently helped than those of chronic nasal congestion.

ASTHMA Results in these cases are disappointing. Approximately 10 to 30 per cent of asthmatics in our experience obtain a beneficial effect from the drugs. These agents appear to be of greater benefit in relieving the spasmodic type of cough associated with asthma, especially that frequently seen in children. Where benefit is observed in asthma, the degree of symptomatic improvement is usually not as striking as that obtained from older remedies such as epinephrine, ephedrine, aminophyllin or iodides.

MISCELLANEOUS CONDITIONS The effect of the antihistamine drugs in allergic headache and gastrointestinal allergy has in our experience been quite inconstant.

SIDE ACTION

A relatively high incidence of unpleasant side effects is a major difficulty in the use of antihistamine drugs, and has limited their usefulness in many cases. From present evidence at least, it appears that toxicity studies in animals are not reliable guide to the occurrence of side action in man. Several of the newer compounds exhibit less unpleasant effects, and in some instances this is accompanied by a diminution in therapeutic effectiveness. Drowsiness is the most frequent untoward action. Vertigo, headache, fatigue, as well as evidence of central nervous system stimulation are also commonly seen. Gastro-intestinal symptoms are frequent with some drugs but may be minimized by taking the medication when food is in the stomach. The combination of these drugs with amphetamine, caffeine, and other stimulants has been recommended in overcoming drowsiness. With the availability of a number of new drugs it is very likely that a trial of several of these will reveal a compound that is well tolerated by the individual patient. To date there have been relatively few reports of serious toxic side effects from the use of these drugs. It must be remembered, however, that with wide usage over longer periods of time more evidence of chronic toxicity may become evident.

CLINICAL EXPERIENCE WITH NEWER COMPOUNDS

ANTISTINE (Ciba) This compound possesses a basic structure similar to that of Antergan, differing chemically only by the substitution of an imidazolin ring for the ethylenediamine radical. Antistine has been in clinical use for some time in Switzerland and other European

countries with considerable success. In our own experience the drug exhibits less undesirable side action than many drugs currently in use in this country. In equivalent doses it is somewhat less active than Pyribenzamine. Its low toxicity, however, allows it to be employed by many patients in doses of 50 and 100 mg with good symptomatic effect. On the basis of our recent evaluation of this compound, the clinical action of a 100 mg dose appears to be equivalent to a 50 mg dose of Pyribenzamine. Antistine is somewhat less irritating to mucous membranes than several other compounds tested, and may be effective when applied topically in the eye or nose in the form of a 0.5 per cent buffered solution. Combined with a vasoconstrictor such as Privine 0.025 per cent, the decongestant action of the drug on the allergic nasal mucosa in many instances appears to be more intense and prolonged than from either solution alone.

NEOANTERGAN (Merk) This drug is closely related chemically to Pyribenzamine, differing only by the addition of a methoxy radical to the benzene ring. Experimentally we have found this drug to be considerably more active than Antergan, Benadryl or Pyribenzamine in preventing fatal histamine shock in guinea pigs. Such wide variations are not apparent in anaphylactic shock. We have used the drug clinically with good symptomatic effect in a large group of representative allergic patients, employing doses of 50 and 100 mg. The incidence of side action in over 100 patients who received the drug was 21.9 per cent. No evidence of chronic toxicity was observed in our series. One patient received 200 mg daily for six months while another took 400 mg daily for a period of five months without significant changes in blood count, urine, or liver function.

NEOHETRAMINE (Nepera) This drug differs structurally from Neoantergan by replacing the pyridine radical with a pyrimidine ring. Clinically, Neohetramine has an advantage over all other antihistaminics investigated, in that it is extremely well tolerated, and may often be used successfully in patients who are unable to take other drugs of this series because of unpleasant side action. In a series of 170 patients who received this drug for various allergic complaints, side effects, relatively mild in nature, were encountered in only 12.1 per cent. Repeated blood, urine and blood pressure examinations in those receiving the compound over long periods failed to reveal any evidence of chronic toxicity. Clinical effect was found to be best when doses of 100 mg were employed.

THENYLENE (Abbott) or HISTADYL (Lilly) This compound which is manufactured under two different trade names resembles Pyribenzamine in chemical structure, except for the replacement of the benzene ring by a thiophene radical. This alteration in structure results in less protection against fatal histamine shock in guinea pigs on the part of the newer compound, but does not appear to lessen its antianaphylactic ability. Clinical results in a large series of patients who received this drug compared favorably with those obtained from other known antihistaminics. Side effects from doses of 50 mg were less frequent than from equivalent doses of benadryl, pyribenzamine or neoantergan. Greater clinical activity was apparent with doses of 100 mg although side actions became more apparent when larger amounts of the drug are used. No evidence of toxicity was observed.

in patients receiving this drug in amounts of 200 to 400 mg daily for periods of 8 to 10 weeks

TAGATHEN (Lederle) This compound is similar in chemical structure to Thénylene or Histadyl, differing only by the addition of chlorine atom to the thiophene ring. This alteration is reported to increase the antihistaminic powers of Tagathen in the experimental animal. Our own clinical experience with this drug indicates that excellent symptomatic action with a low incidence of side effects is obtained from 50 mg doses of the drug.

THEPHORIN (Hoffman-La Roche) This drug differs in chemical structure from all other known antihistaminics. Experimentally Thephorin is active in abolishing the pharmacologic effects of histamine. We have observed a satisfactory symptomatic effect in many allergic syndromes with doses of 10 to 50 mg with very little evidence of severe side action. The drug is supplied in the form of 25 mg tablets and as a palatable elixir, containing 10 mg of the drug per 4 cc. The latter form is especially suitable for use in young infants and children.

BENADRYL-PARENTERAL (Parke-Davis) This drug is now available in solutions containing 10 mg per cc, designated for parenteral use. The usual mode of administration is intravenously, although it may also be given intramuscularly. It is slightly irritating when given subcutaneously. This form of Benadryl is indicated where oral antihistaminics are without effect or cannot be given. In some patients small doses produce a marked hypnotic effect, and, therefore, the initial intravenous dose in each patient should be given cautiously. One cc may be given to determine the patient's response, and subsequent doses increased up to 5 cc depending upon the requirements of the patients.

PYRIBENZAMINE OINTMENT 2 PER CENT (Ciba) This drug incorporated in a water washable or anhydrous ointment base is a valuable aid in obtaining relief of itching in such disorders as atopic dermatitis, contact dermatitis, and pruritis ani. In our own experience, the drug incorporated in the water washable base is more apt to be effective than the anhydrous preparation.

LIMITATIONS OF ANTIHISTAMINIC THERAPY

It should be emphasized that the antihistaminic drugs are purely palliative medication. They produce no lasting benefit and possess no curative effects. Chronic symptoms usually recur a short time after withdrawal of the drugs. There is little evidence to support the contention held by some writers that continued use of the medication for a time prior to the expected onset of symptoms will be of greater benefit. Inasmuch as the effect of a single dose is of relatively short duration, they should only be employed where active symptoms warrant their use. The use of these drugs is not a substitute for careful immunologic study necessary in each case of allergy. The determination of specific etiologic factors, the elimination of the offending allergens where possible, or hyposensitization when necessary, are the sole means at present of achieving lasting results in allergic disease. The antihistaminics are valuable symptomatic drugs which may frequently afford the patient temporary relief from his discomfort until the effects of more specific therapeutic measures become evident.

(From *American Practitioner*, June 1948)

Critical Notes and Abstracts

STREPTOMYCIN TREATMENT OF BUBONIC PLAGUE— Iladdad, C, and Valero, A, British Medical Journal, May, 29, 1948

Streptomycin treatment of three very severe cases of plague not responding to sulphonamides resulted in speedy recovery. A fourth severe case was not treated with streptomycin, and the patient died on the eighth day of his illness. Whereas the effect of streptomycin on the general condition of the patients was remarkably good, the buboes appeared to be uninfluenced if treated late. This was true also in respect of the sulphonamides, and in most cases incision and drainage were necessary to bring about resolution.

ORAL "MYANESIN" IN TREATMENT OF SPASTIC AND HYPERKINETIC DISORDERS—F M BERGER, M D and R P SCHWARTZ, M D Rochester, N Y J A M A 1948

The interesting pharmacologic properties of "myanesin" (8-orthotoloxyl-1, 2-propanediol), such as its power to relax spasticity and rigidity, its action to restore deranged reciprocal innervation and its inhibiting effect on certain release symptoms, suggested that this drug may be useful in the production of muscular relaxation during anesthesia and for the treatment of certain spastic and hyperkinetic disorders. "Myanesin" has since been widely used for muscle relaxation during anesthesia in Great Britain, and it was recently reported that 10,000 patients received intravenous injections of this agent.

The value of "myanesin" in the treatment of spastic and hyperkinetic disorders has not been examined as extensively. Stephen and Chandy obtained short-lived beneficial effects on certain diseases of the extrapyramidal nervous system on intravenous administration of a 10 per cent solution of the drug. They also observed localized thrombophlebitis and transient hemoglobinuria following administration. These side effects were due to the solvents used in the preparation of concentrated solutions of "myanesin". Schlesinger and associates observed that the use of 2 per cent solutions of "myanesin" caused neither phlebitis nor hemoglobinuria on intravenous administration, it ameliorated involuntary movements, rigidity, spasticity and tremor. The drug was, however, of limited clinical value because of its evanescent action and the alleged ineffectiveness after oral administration. The purpose of this report is to draw attention to the fact that "myanesin" is well absorbed after oral administration, and to outline briefly the satisfying results obtainable in previously intractable conditions.

The drug was administered as 8.8 per cent (weight in volume) solution in 20 per cent (volume in volume) aqueous propylene glycol, with syrup of cherry 20 per cent (volume in volume) to improve the taste of the mixture. The usual single dose was 30 cc of the mixture equal to 1 Gm of "myanesin". Children received proportionally smaller doses. To obtain objective and permanent evidence of the effect of the drug electromyographic records were taken prior to administration of the drug. "Myanesin" was then administered without disturbing the leads and muscular activity recorded thirty to sixty minutes after administration of the drug. The disappearance or diminution of the abnormal muscular discharges in the electromyograms

could be observed as soon as five to twenty minutes after administration of the drug. These changes were as a rule accompanied by other signs and symptoms, such as decrease of spasticity, increase of range of motion, amelioration of involuntary movements and relief of pain.

The rapid absorption of "myanesin" from the stomach could be demonstrated by the presence of metabolic products of "myanesin" in the urine as soon as fifteen minutes after oral administration of the drug. The metabolic product gave a cherry red colour on treatment of the urine with Ehrlich's diazo reagent. "Myanesin" itself did not give this reaction. Those workers who found the drug ineffective on oral administration presumably administered it in tablet form.

Hemiplegic patients whose paralysis has been stationary for four to seven years showed striking recovery of some of the voluntary movements of the paralyzed limbs ten to twenty minutes after administration of the drug. The maximum benefit was usually obtained after two to three days of medication and could be maintained by giving 1 Gm doses in the mixture three to five times daily. These observations show that loss of function in spastic paralysis is not necessarily or exclusively due to the destruction of motor pathways. It is possible that loss of movement in residual paralysis in apoplexy and spastic paralysis in general may be primarily due to the splinting action of spasticity. Spasticity is caused by an exaggeration of the stretch reflexes. The power of "myanesin" to bring about a return of function in spastic paralysis is due to its property of reducing exaggerated reflexes to normal without affecting the normal reflexes. In this way spasticity may be reduced without abolition of voluntary power.

Remarkable results were also obtained in certain cases of cerebral diplegia. The drug appeared effective in spastic, athetoid and choreiform types of the disease. In spastic diplegia the drug, in the doses given, caused but little diminution of spasticity as judged by the increased tendon jerks and clonus. Manipulation of the spastic limbs was, however, easier, and the physical performance of the patients improved. They were able to walk more quickly and for longer periods of time than before administration of the drug. The choreiform jerking movements were ameliorated to a somewhat greater extent than the slower athetoid movements. Some of these patients had lesions which were particularly sensitive to the drug. The athetoid movement and inco-ordination of a woman, 21 years of age, were almost completely controlled by a single 0.5 Gm dose, but other patients derived less benefit from larger doses repeated several times daily. One patient (a woman of 22 years) while receiving "myanesin" (1 Gm thrice daily) showed signs of decerebrate rigidity, which subsided again after discontinuance of the drug. The administration of smaller doses (1 Gm once daily) ameliorated athetosis and did not cause side effects. The favorable effect of "myanesin" in diplegia is due to the depressant action of the drug on the nuclei of the brainstem and to its power to re-establish disturbed reciprocal innervation, which also plays an important part in the clinical picture of the disease. The amount of benefit derived will also depend on the exact localization of the cerebral lesions.

In Parkinson's syndrome the oral administration of "myanesin" reduced tremor and rigidity. The effect of the drug on oral administra-

tion was not as spectacular as that observed after parenteral administration, but it was of longer duration and did not cause side effects. The best results were obtained if "myanesin" was given in addition to the usual drugs of the atropine class. Certain patients derived only little benefit from the medication. This may have been due to too low a dosage, incomplete absorption or insensitivity of the pathologic mechanism to the drug.

The oral administration of "myanesin" also proved effective in various conditions causing muscular spasm, such as arthritis of the cervical part of the spine (fifth and sixth cervical vertebrae), subacromial bursitis, pain low in the back, osteoarthritis of the hip joint and similar conditions. "Myanesin" frequently relieved both spasm and pain due to spasm. Sometimes the action was transient and of short duration, and sometimes it was prolonged indefinitely. In the latter case this effect was thought to be due to an interruption of a pain-spasm vicious circle. "Myanesin" did not have any central analgesic action of the type possessed by morphine or meperidine hydrochloride, but had anti-pyretic properties of a similar or greater order than the salicylates. The effect of the drug in acute rheumatic fever would be of interest. "Myanesin" was ineffective in contracture due to ischemia, multiple sclerosis and thromboangitis obliterans.

The oral administration of "myanesin" rarely caused side effects. Blood pressure, heart rate and respiration were not affected. Nystagmus, diplopia, mild muscular inco-ordination and other symptoms sometimes appearing after intravenous injection were not observed after oral administration. Only 1 out of the 59 patients treated thus far complained of anorexia. Nausea or vomiting were not complained of. Several patients experienced a transient feeling of lassitude for ten to twenty minutes after administration. This lassitude was not, however, great enough to prevent them from carrying out their usual duties. Samples of blood were frequently examined for hemoglobinemia with negative results. The results of the Van den Bergh test were always within normal limits. The urine remained free from protein and blood in all cases, but always showed a positive reaction to the Ehrlich diazo test. The intensity of the color obtained with the urine was proportional to the amount of "myanesin" taken. Certain patients have now been on continuous medication for five weeks without showing side effects. Patients receiving the drug should, however, be watched closely, as the chronic effects of the drug on human beings are still unknown.

The benefit obtainable with oral administration of "myanesin" in spastic and hyperkinetic disorders is much greater than that obtained with curare, erythroidine, neostigmine or any other known remedy. But, there is a need for other drugs possessing a still stronger spasticity-releasing action. This preliminary communication is presented in the hope that it will make the life of those who cannot move as they wish more tolerable and stimulate interest in research designed to increase the understanding and essential resources for control of abnormal functions of the central nervous system.

Conclusions The ortho tolyl ether of glycerol called "myanesin" has a relaxant effect on muscle spasm, spasticity and rigidity and an ameliorating effect on tremor and involuntary movements of extrapy-

ramidal origin. These effects are caused by a selectively depressant effect of the drug on the central nervous system. Up to the present the drug has been administered intravenously and was thought to have little practical interest because of the evanescent action and side effects introduced with this route of administration. The present report shows that "myanesin" on oral administration produces most of the beneficial effects observed after intravenous administration without causing side effects. The drug was well tolerated over a period of many weeks and favorably influenced several previously intractable conditions.

Book Reviews and Notices

MEDICAL ANNUAL 1947 A Year Book of Treatment and Practitioner's Index 65th Year. Editors: Sir Henry Tidy and A. Rundle Short. Bristol: John Wright and Sons Ltd. Pp 464. Art plates 43. Price

In spite of continued production difficulties, the Medical Annual has entered the sixty-fifth year maintaining its usual excellent standard. The contributors being persons of high repute in their own branches, the standard of reviews is very high. Special mention must be made on the recent developments in occupational health. It is not enough to treat industrial diseases. It is important to realize that prevention of sickness and promotion of better health is far more desirable in every field to carry out work effectively. Advances in chest surgery has opened up a new field for the surgeon which was until now only the realm of the physician. It is more and more realized that medicine and surgery are not two different fields but are complementary parts of one another. Greater co-operation between physicians and surgeons being necessary, the inclusion of surgical reviews in the Medical Annual is of great advantage to both. The Annual is a useful book both for the specialist and the general practitioner who wants to keep in touch with modern trends of thought. The Practitioner's Index is a very useful ready reference for the busy practitioner. The plates and simple figures make for a clearer understanding. U M

REVIEW OF TROPICAL DISEASES A Handbook for the Practitioners in the Tropics. Editor N G Majumdar. Calcutta. Publishers S C Sarkar & Sons Ltd, 1, College Square, Calcutta-12. Pp 374. Price Rs 12.

As the first of its kind in India the attempt is commendable yet it has a far way to go to reach the excellent standards maintained by the Year Books and Annuals from abroad. The volume is divided in six sections. The first, the magazine section contains four long articles on History of Medicine in India, Enteric group of Fevers, Tropical Eosinophilia, (rather a sketchy superficial review of the subject, giving nothing new and neglecting many well-known references in the literature), and Fats and Oils in Indian Diet. The second section gives six long articles by American writers on Malaria, Rickettsial Diseases, Diarrhoeal Diseases, Roentgenologic Changes in Tropical Diseases, Treatment of Resistant Kala-Azar (by Sen Gupta) and DDT. The third section contains therapeutic notes on sulphonamides, anti-

biotics, penicillin, streptomycin, prescription writing and useful drugs. The fourth section gives practical abstracts on common tropical diseases. The fifth section of 2 pages reviews four books and the last section called the practitioner's guide contains a list of some 15 proprietary preparations. We believe that as a review for the busy practitioner, the volume will lose much of its value if the articles are too long. What is more needed is a brief resume of original work done on tropical diseases. For the specialist there is little in this book to recommend it. A more complete index would be more appreciated. We hope that the second volume will attain a better standard. U M

THE INTERNATIONAL JOURNAL OF SEXOLOGY incorporating **Marriage Hygiene**
Vol II No 2 August 1948 Editor A P P Pillay Whiteaway Bldg Hornby Road, Fort,
Bombay pp 70 Annual Subscription Rs 12 Sh 22/- £ 5 50

This Journal published quarterly, fills up a void in medical literature. Little knowledge is given to the medical student in sex education and marriage hygiene. Few books are read by them on sexology. Yet the practitioner constantly comes across problems which he would be more competent to solve if he had better information. A journal of this type should be more widely circulated. In addition to the already existing features we would appreciate a 'question and answer' corner where the difficulties encountered by many practitioners would be answered by competent authorities. We recommend this journal to the general practitioner. We hope that the journal will maintain its high standard. U M

YEAR BOOK OF PEDIATRICS 1947 Editors: I A Abt. and A. F. Abt. The Year Book Publishers Chicago Pp 436 Price \$ 3 75

The 1947 Year Book of Pediatrics maintains the high standard for which the Year Books from Chicago are known all over the world. Advances in various fields of diagnosis and treatment are so rapid that practitioners are apt to neglect this one field which should be given prime importance. The Year Book brings to all keen on keeping in touch with advances in Pediatrics, a rapid resume of current literature on the subject. We draw attention to articles on Infectious Hepatitis in children, Cystic Fibrosis of Pancreas with purulent respiratory tract infection, Celiac Syndrome, Water Balance as Pediatric Problem, Meningitis in children, Sudden Death in Rheumatic Fever (due to acute anaphylactic coronary angitis), Rubella in Pregnancy causing Congenital Malformations, Polomyelitis and Prostigmune.

Kugelmass recommends use of androgens with restriction of fluids and psychotherapy in Familial Enuresis. Re-education of the parents and child rather than a dietary, medical or surgical treatment is stressed by Sweet. Roosen-Runge stresses the involvement of the liver with fatty infiltration in patients with Mongolism and in patients with Hydrocephaly and Microcephaly. Cummins and Platon state that early diagnosis of Mongolism can be made with about 90 per cent accuracy through use of hand prints.

The value of Penicillin in pediatrics is well established and necessary doses for oral and parenteral use are recommended. More information is given on Rh factor and the sequence of events leading to erythroblastosis. This Year's volume is dedicated to Dr Issac Abt, the able editor of the Year Book of Pediatrics for the last 46 years, who enters his eightieth year. We join the publishers in felicitating him. U M

Reflections and Aphorisms

THE DOCTOR'S JOB

"It is only a few years since doctors came out from behind the ambush of their beards, not so many since they laid aside their frock coats and topplers, their peaked Merlin caps and robes, their priest's vestments, their barber's aprons, their horrendous masks and drums. Today it is only taxi drivers who recognize us by the cut of our jibs. We move among laymen, stamped by no hallmarks, followed by no wake of disinfectant. No longer are we extolled as the flower of society, or ridiculed as quacks and charlatans. We are pretty much accepted for what we are—human beings with human frailties, possessing certain expert knowledge of which society has need. If we have sensitivities and mores of our own they are, in the main, looked upon indulgently as harmless vestiges.

"We have, in truth, helped to unfrock ourselves. As we have forfeited our "props" and even our bedside manner, so, at the same time, have we tried to share our knowledge with others. It is now no uncommon experience for a doctor to read of an important medical discovery in the columns of his morning paper, or to learn about the use of some new drug from a "detail man" representing one of the big pharmaceutical houses. How different this from the day when we were the sole possessors of an esoteric cult, from the day when we were elite among the literati, when our title implied that we were eminently learned men and not chiroprodists or chiropractors.

"In many respects, so it seems to me, the doctor's job is changing. He is becoming more of a teacher in conformity with the archaic meaning of the title—and less of the wizard who compounds the serpent's wisdom and the dove's harmlessness. He is less engaged than once he was with the exorcism of evil spirits and more with the prevention of illness and with efforts to restore deranged bodily and mental functions. He is sharply aware of his own ignorance, in the face of many unsolved mysteries. And he accepts, with late Mr. Justice Holmes, the dictum that "*to live is to function*." He is a mechanic—a serviceman, a repairman who instructs others in maintenance and upkeep. It is not for him to ask whether the machine is worth saving or whether its usages are noble ones. He knows something of what Thomas Huxley called "the rules of the game"—a nice Anglicism for the Laws of Nature—which govern not merely things and their forces but men and their ways as well. These the doctor attempts to impart to others less instructed than himself. "*Knowledge goes to the help of Everyman*." As he sees humankind in its nakedness, in its fear and weakness, in its suffering and despair, he is forced into a uniquely personal relationship. He is the harbinger of birth and often death's mighty messenger—Death, to whom Everyman says "Thou comest when I have thee least in mind."

"His lineage is an ancient one, his task formidable. Stemming from medicine-man and witch-doctor, his face is now set against superstition, magic and black art, and yet he is inexorably caught up in the ignorance and bigotry of his own time. Although he began as a simple conjurer he gradually assumed the character of tribal chief and king. He became a mangod, a human being endowed with divine or supernatural powers.

"In the evolution of primitive societies he constituted the oldest artificial or professional class. But the profession of exorcist has never been safe from intruders. There are always upstarts and outsiders who lay claim to healing powers—quacks, wonder workers, nature healers, patent-medicine vendors and kings. (You will recall that the young Samuel Johnson was taken before Queen Anne to be cured of scrofula.)

"In medicine's struggle with ignorance and superstition, magic gives way to religion and religion to the method of science. But always the cry from the afflicted is the same: "Help us! Heal us! Cure us! Our suffering is greater than we can bear." And the doctor is forced into the role of god-man of Imhotep who through sacrifices restores the waters to the parched valley of the Nile, to whom the sick repair for cures, or again of Aesculapius migrating from his deep subterranean cleft in Thessaly, with his companion the Serpent, to the island of Cos, where altars were established in his honour, or even of a Christlike figure who says: "Come unto me, all ye that labor and are heavy laden."

"Our patients are often sceptical. They demand miracles of us. They limit our moves by making pawns of us—or kings—when we should range freely as knights. Like other men we have to struggle for our living and do battle for our professional standards and for the scientific truth. These we fight for gladly. It is indeed a poor heart that never rejoices."

—CARL BINGER, M.D. (THE DOCTOR'S JOB)

"Alas, the general physician of the type who taught me and my father at Guy's has become a *rara avis*. The logical attitude and thoughtful integrations of ideas and subjects are tending to go by the board. The new technology and over-specialization has led too often to a neglect of the philosophy which could co-ordinate all our sciences and methods. We have, in brief, gone astray in no small measure because of the multiplicity of our new tools and tests and our impatience to employ them. Meanwhile we are suffering—and our patients with us—from a very serious dearth of men and women with a *physicianly training and physicianly minds*, of men like the old *chef de clinique* and the good family doctor, of men like Balzac's hero in *Le Medecin de Campagne*."

—Prof A. J. RYLE

The Indian Physician

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WHOLE NO 82

Original Contributions

FURTHER OBSERVATION ON SYMBIOSIS OF MICROORGANISMS IN CULTURE WITH SPECIAL REFERENCE TO MYCOBACTERIUM IN LEPROSY

by

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In a previous communication (1), it was reported in 1946 that it is possible to isolate in pure culture, acid fast micro-organisms derived from the infected lesions in Leprosy, by inducing them to grow in *company with a protozoan (Leishmania) in culture*. These results have been confirmed by repeating the old experiments, this year (Fig I and Fig IA). Here, it is proposed to record some observations on their symbiosis with some *culturable bacteria*. For this purpose an easily culturable acid fast bacterium was selected for the active agent of the process, in the place of a protozoal (*Leishmania*) culture. It was felt that such a companionship would presumably yield an equally successful result. There being at least some points in common to both the microbes used in the experiment, *viz* general morphology and staining characters, one would naturally expect that the simple metabolites elaborated from the complex food material, essential to the growth of the culturable active agent would be even more congenial and beneficial to induce the proliferation of the inert mycobacterium than what obtained in the previous experiments with a protozoan as an active agent.

Before proceeding to put these considerations to the experimental test a preliminary observation was made by planting in the haemoglobinised saline solution a few drops of serosanguineous fluid derived from a well marked subcutaneous leproma along with a trace of a non-leprous acid fast bacillary culture and incubating the mixture at 20°C. The non-leprous acid fast bacillary culture, be it noted, was the one which had been condemned as being a possible saprophyte or a contaminant occurring in the early symbiotic experiments of 1946, after some weeks of incubation at 20°C with periodic renewal of the nutrient, it was planted on Glycerinated potato and incubated at 37°C. Three weeks later, a pale yellow culture of acid fast bacilli (some long and other short) was obtained which was obviously a mixed culture, as was to be expected. After a time the culture became deeper in colour almost to orange, but the remarkable feature was that its surface

was a crowded mass of heaped up small spheroidal colonies resembling a culture of *Mycobac tuberculosis*, twice and three times magnified but yellowish orange in colour (Figs II and IIA). These characters strongly suggested that it was probably brought about only by symbiosis of the *Myco leprae* with a *non-leprous acid fast bacillary* culture. But the isolation of the two *Mycobacteria* of the mixed growth by subculture etc was found exceedingly tedious and almost impracticable. To meet this difficulty the following technique was devised and found satisfactory. An Ehrlemmeyer flask of about 200 c.c. capacity into which a suitable Pasteur Chamberland filter bougie had been introduced was sterilised after properly plugging it with cotton wool. The flask was then filled to the depth of 2.5 cm. with a nutrient fluid (Sauton) favourable to the growth of acid fast *Myco tuberculosis*. This was followed by the introduction into the bougie of a small fragment of the spleen of a mouse well infected with *Myco stefanski* and then the fluid outside the candle in the flask was inoculated with a loopful of *Myco tuberculosis* culture taking great care not to touch the bougie during the manipulation. This was the unenturable *Myco stefanski* was induced to grow side by side with *Myco tuberculosis* in the same nutrient fluid, but separately, it being confined inside the bougie whose walls were bacteria-proof but freely permeable to the diffusible substances likely to be generated by the *Myco tuberculosis* growing outside (such substances being amino-acids salts etc. and even enzymes) (Fig IV).

At the end of four weeks at 37°C it was found that the *Myco tuberculosis* had grown luxuriantly with a thick scum covering the surface of the fluid in the flask outside the bougie, while the contents from inside the bougie were to the naked eye clear and free from any obvious growth but microscopically it showed a few sparingly distributed longish acid fast bacilli (expected to be derived from the macerated bits of the infected spleen previously introduced). A drop from this fluid was plated on the surface of the glycerinated potato and with another drop, was inoculated a tube of Sauton culture fluid for control. 8 weeks later (at 37°C) a small yellow patch was noted on the potato surface which on examination showed that it was pure culture of acid fast bacilli now perhaps a little shorter than the original. It is evident that the *Myco stefanski* has definitely proliferated inside the bougie in symbiosis with a bacterium (*Myco tuberculosis*) though not in its intimate contact (Fig III). The control tube inoculated at the same time showed no growth and therefore the walls of the bougie were bacteria-proof.

To conclude these results prove that acid fast *Mycobacteria* can be isolated in culture by symbiosing leprous material with culturable micro-organisms whether they are *mycobacteria* or *protozoa* in culture makes no difference. It may be repeated here as to how far this culture isolated by symbiosis from the spleen of the mouse infected with *Myco stefanski* is also those isolated from human lepromata and rat leprosy by symbiosis with protozoa will go to fully satisfy Koch's postulates and also how their identity can be established, is left for future investigation.

REFERENCE

Row R (1946) Isolation of *mycob leprae* in culture (Lecture) Indian Physician, April 1946

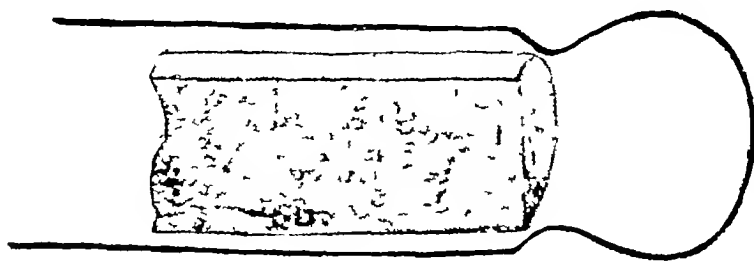


Fig I

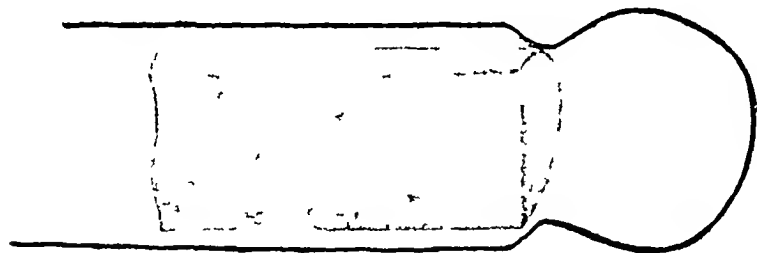


Fig I A

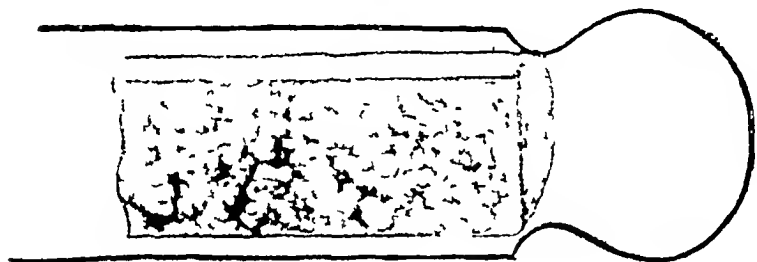


Fig II



Fig II A

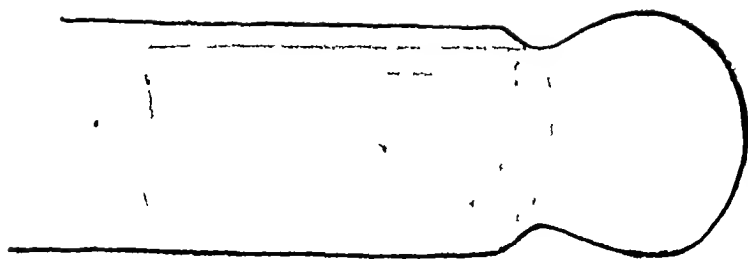


Fig III

[For explanation of Figs P T O

PLATE II

Row—Symbols of Microorganism

Fig I Infecting Material Human Leprosy of 27.2.48
A four weeks old acid fast *Mycobacterium* sub culture on glycerinated potato at 37°C isolated from symbiosis of *Mycobacterium* leprae with a protozoan in culture in haemoglobinised saline at 20°C for 6.8 weeks, first appearance on potato 3 weeks

Fig 1A Infecting Material Rat Leprosy of mouse 1.8.47
A four weeks old acid fast *Mycobacterium* sub culture on glycerinated potato at 37°C isolated from symbiosis of *Mycobacterium* *stefanski* with a protozoan in culture in haemoglobinised saline at 20°C for the same period, first appearance on potato 3 weeks

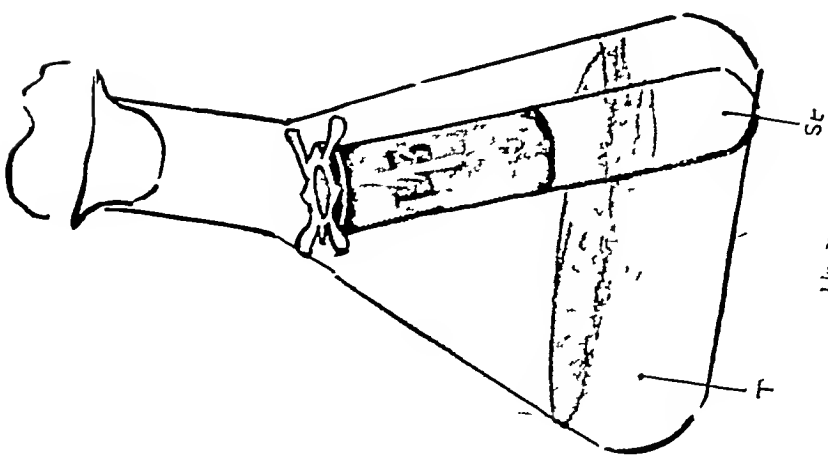
Fig II Infecting Material Human Leprosy of 21.8.48
A four months old mixed acid fast *Mycobacterium* sub culture on glycerinated potato isolated from symbiosis of *Mycobacterium* *leprae* and a non leprosy acid fast *Mycobacterium* saprophyte in haemoglobinised saline for 10 weeks at 20°C, sub culture has darkened

Fig IIA Infecting Material Leprosy of 12.11.46
A four months old sub culture of the acid fast *Mycobacterium* non leprosy saprophyte of the same age isolated on glycerinated potato at 37°C in haemoglobinised saline at 20°C, for the same period of 10 weeks, control of fig No II culture has darkened by age

Fig III Infecting material Rat leprosy of mouse 7.5.48
A two weeks old sub culture of acid fast *Mycobacterium* on glycerinated potato at 37°C isolated from a modified symbiosis of *Mycobacterium* *stefanski* in haemoglobinised saline with *Mycobacterium* tuberculosis at 20°C for 8 weeks, control of fig 8 weeks on potato at 37°C

Fig IV Apparatus used for modified symbiosis of *Mycobacterium* *stefanski* with *Mycobacterium* tuberculosis
A two weeks old sub culture isolated on glycerinated potato at 37°C are chronic into short almost co-bacillary forms, that derived from human leprosy, however, bundle shaped aggregates (also shorter than the original) and many disposed off in cigar shape. Microscopically All these cultures show the acid fast *Mycobacterium* but altered is distinctly bacillary (also shorter than the original) and many disposed off in cigar shape. Microscopically All these cultures show the acid fast *Mycobacterium* but altered is distinctly bacillary (also shorter than the original) and many disposed off in cigar shape.

1 in 11



CARDIAC DYSPNOEA

A PHYSIOLOGICAL APPROACH TO ITS PATHOGENESIS (WITH A REVIEW OF THE MEDICAL LITERATURE)

by

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Physiology has made some very rapid strides, of late, in the matter of cardiac dyspnoea. From the standpoint of medical literature, few subjects in medicine have been more evocative or fruitful than cardiac dyspnoea, there being well over a thousand publications on this subject alone. In spite of the massive bulk of the literature, our knowledge, far from being explicit, continues to remain controversial and disseminated. The literature, which had originally started as a stream, has now become a veritable flood. The inquisitive reader in quest of knowledge who embarks for the first time upon a perusal of the literature on cardiac dyspnoea, more often than not makes a hasty retreat, overwhelmed by the immensity of his task. However, in this exuberant mass of verbiage, there are certain contributions or papers, such as those of Harrison and his associates, Peabody and others, which stand shoulders above the greater majority, like "oases in a desert of unreadability."

The object of the present monograph is to present to the members of the medical profession a formulated summary or resumé of the present-day views and theories on the subject of pathogenesis of cardiac dyspnoea.

In order not to deter from this object and also for the sake of brevity, it has been considered desirable to exclude from the present discussion, the "non-cardiac forms" of dyspnoea as well as the symptomatology and therapeutics of the cardiac forms.

To the average individual, the word "dyspnoea" implies a state of "breathlessness" or "shortness of breath." Meakins⁸⁴ has defined dyspnoea as "the consciousness of the necessity for increased respiratory effort." Though this definition suggested by Meakins is undoubtedly the most accurate from the etymological point of view, nevertheless, it fails to exclude cases of "breathlessness" in unconscious individuals, hence, Christie^{16A} prefers the use of a more elastic definition for dyspnoea and regards the latter condition as "a conscious or visible increase in respiratory effort."

Recent observations suggest that dyspnoea is not merely one single sensation or sensory impression but is probably "a summation of numerous sensory impressions," "a complex sensory phenomenon." The peculiar feeling of "pressure" or "tightness" in the chest, epigastrium and neck that is so frequently associated with the symptom of dyspnoea has been attributed by Goldscheider and others⁴⁶ to an increase in tone of the intercostal and diaphragmatic muscles. Another peculiar feature or sensory impression that is frequently associated with the subjective discomfort of dyspnoea is a "sense of fatigue" or tiredness of the chest-muscles, this has been ascribed by Fishberg⁴⁰ to "overwork" or excessive use of the muscles.

of the chest and diaphragm during the respiration of dyspnoea. There is no doubt that psychological impressions *e g* sensations of dread and fear of choking, are frequently combined with the principal sensation of dyspnoea.

THE PRIMARY, ESSENTIAL OR FUNDAMENTAL FACTOR OF IMPORTANCE IN CARDIAC DYSPNOEA

Though an innumerable variety of factors and mechanisms have been incriminated, either individually or jointly in the genesis of dyspnoea as will be obvious from the following discussion, it has been proved by Harrison⁵¹ that the *essential* mechanism finally concerned in the causation of dyspnoea is an increase in the so called "ventilation index" or a decrease in "respiratory reserve".

From the pioneer investigations of Peabody and his colleagues⁹⁰ and of Harrison and co-workers⁵¹, it appears that the severity of dyspnoea in individuals with heart disease bears some sort of relationship to the ventilation or volume of respired air on the one hand and to the vital capacity on the other, it appears to be directly proportional to ventilation and inversely proportional to vital capacity. According to Harrison⁵¹, these parallelisms are very rough indeed, he finds that a much more accurate measurement of the degree of dyspnoea is furnished by a correlation of these two factors (*viz* ventilation and vital capacity) rather than by the consideration of any one factor alone. In his opinion, the degree of dyspnoea is closely related (in direct proportion) to the quotient— $\frac{\text{Ventilation}}{\text{Vital Capacity}}$. In order further to correct this formula for the nutritional state of the patient (the state of obesity), Harrison and his co-workers⁵¹ have evolved a more accurate quotient or formula for the measurement of dyspnoea (the so-called "ventilation index" of Harrison)

$$\text{Ventilation Index} = \frac{\text{Ventilation}}{\text{Vital Capacity}} \times \frac{\text{Ideal Weight}}{1 + \frac{\text{Actual Weight} - \text{Ideal Weight}}{2}}$$

These workers also believe that dyspnoea is essentially a "threshold symptom" which will arise no sooner the value of the ventilation index attains or exceeds a certain threshold value. From a vast experience of dyspnoeic patients, they conclude that threshold for dyspnoea, in the great majority of cases (excluding cases of neurosis), corresponds to a value of 25 to 30 of the ventilation-vital capacity quotient. Below the value of 25, there is usually no dyspnoea, with values ranging from 25 to 35, there is usually mild distress, with values from 35 to 45 moderate distress and with values over 50 severe distress.

In a given cardiac patient, therefore, dyspnoea arises if the value of the ventilation index exceeds the "dyspnoea threshold" and thus may be brought about by an increase in ventilation (hyperventilation or over ventilation), by a decrease in vital capacity or as is most often the case, by a combination of these two factors.

The same fundamental fact about dyspnoea has been expressed in a different manner by other writers on the subject. They ascribe dyspnoea to a diminution or impairment of the so-called "Respiratory factor of safety" or the "Respiratory Reserve". The latter has been defined as the difference between "the volume of air breathed per minute" and "the maximum minute volume of ventilation possible".

(Fishberg⁴⁰) In cardiac patients this factor gets less owing to an increase in the "volume of air breathed per minute" and a decrease in the "maximum volume of air that can be breathed within one minute" In other words, a limitation or impairment of the respiratory reserve will arise with resultant dyspnoea if there is sufficient increase in the volume of ventilation, a sufficient decrease in vital capacity or a combination of these two factors

CAUSATIVE FACTORS OR PRIMARY MECHANISMS CONCERNED IN THE GENESIS OF CARDIAC DYSPNOEA

Innumerable factors or mechanisms have been incriminated from time to time in the pathogenesis of cardiac dyspnoea, some genuine and some hypothetical For the sake of brevity, these hypothetical factors are excluded from the present discussion and only those factors which have stood the test of time and which are unquestionably involved in the causation of dyspnoea are considered These factors may operate either singly or jointly in the causation of the various forms of cardiac dyspnoea, as mentioned earlier, these factors cause dyspnoea by inducing a rise in "ventilation index"⁵¹ or fall in "respiratory reserve" For want of a better classification the following simple classification based on the mode of action is proposed for the causative factors of cardiac dyspnoea —

Classification of the Causative Factors of Cardiac Dyspnoea

1 Vaso neurogenic Factors *viz* due to the joint operation of vascular and nervous mechanisms

- 1 The "pulmonary factor" *i.e.* engorgement or congestion of the pulmonary vascular tree
- 2 Rise of venous pressure (The Harrison Reflex)⁴¹
- 3 The Carotid Sinus Reflex or the Anoxaemia Reflex of Heymans
- 2 Neurogenic Factors (essentially dependent on a nervous mechanism)
 - 1 Local muscle reflexes
 - 2 Psychogenic factors
- 3 Haematogenic Factors (due to chemical alterations in the nature of blood)
 - 1 Oxygen lack or anoxaemia
 - 2 Carbon dioxide retention
 - 3 Increased pH of blood

THE PULMONARY FACTOR

There is no doubt that of all the causative factors concerned in the genesis of cardiac dyspnoea, this is the most important It is the factor most often concerned in cardiac dyspnoea It frequently acts singly and when acting jointly with other factors, it is usually the principal or most important of the factors

It is of historical interest to know that more than 200 years ago, the dyspnoea of mitral stenosis had been ascribed by Vieussens⁴⁰ to engorgement of the lungs by blood preventing a free access to air In 1811, the great Corvisart¹⁹ attributed cardiac dyspnoea to congestion of the pulmonary vascular tree with blood

In spite of these momentous decisions on the part of men like Vieussens⁴⁰ and Corvisart¹⁹, the medical profession for a period of over a hundred years showed a tendency to digress from the right path and favoured the "chemical theories of dyspnoea" It is only within the last few years, thanks to the pioneer investigations of Peabody,^{40, 43} Harrison^{51, 53} and others, that we have again and rightly learnt to regard "pulmonary congestion or engorgement" as the cause *primum* of cardiac dyspnoea Enough evidence, both clinical and experimental,

has been adduced in an effort to prove the validity of this contention That pulmonary congestion plays a leading role in cardiac dyspnoea is proved by clinical observations like these —(1) Dyspnoea occurs with greatest frequency in cardiac diseases which are most frequently associated with pulmonary congestion *e.g.* left ventricular failure, (2) The frequency with which clinical and roentgenological evidence of pulmonary engorgement can be obtained in dyspnoeic cases of left-sided failure in the event of a super-added failure of the right side of the heart

The physiological mechanisms or factors by which the pulmonary congestion is able to affect the "respiratory reserve" are many and varied —

(1) A diminution in the permeability of alveolar walls⁴⁰ (This factor has been proved by histological studies of the alveoli, by a study of the so called "arterio-alveolar tension difference" and by the inhalation of oxygen in high concentrations)

(2) A reduction in the capacity or size of alveolar lumens within the parenchyma of the lung (This factor has been proved by histological studies, by radiographic appearance and on the basis of animal experiments by Drinker, Peabody and Blumgart)³⁰

(3) Diminished elasticity of lung-tissue (This forms the basis of the "Lungenstarre" or "pulmonary rigidity" theory of Von Basch⁴⁰)

(4) Uneven pulmonary ventilation (Siebeck's theory)^{108,109} (According to Siebeck, ^{108,109} the gas-mixture in the lungs is much less uniform in cardiac cases than in normals and a smaller fraction of the respiratory air is utilized in these cardiac cases The "effective middle capacity" accounts for about 80 per cent of the "true middle capacity" in normals and for only about 50 per cent in cases of heart-failure)

(5) Superficial and shallow respiration, (under the circumstances the "dead space" constitutes a larger percentage of the "total respiratory volume" than in normals, thus leading to impairment of respiratory efficiency)

It was originally suggested by Eppenger and Schiller^{31,32} that pulmonary engorgement may be one of the factors concerned in the reflex stimulation of respiration The validity of this theory has lately been proved by the experiments of Harrison⁵¹ and his associates They were able to induce, in dogs, any desired degree of pulmonary congestion (in one lung) They secured evidence in favour of a "vagal reflex" or "nervous reflex mechanism" in the production of cardiac dyspnoea

That the minute volume of respiration (or ventilation) is increased in cardiac cases, has been convincingly demonstrated by Peabody, Wentworth and Barker⁹³ who found figures as high as 8.5 litres in cardiacs with severe decompensation This hyperventilation may arise through an "increase in amplitude or depth" of breathing or through an increase in respiratory rate In the majority of cardiacs, who exhibit "shallow" rather than "deep" breathing, the second factor is probably all-important

In Fishberg's⁴⁰ opinion, the vital capacity of cardiacs is decreased roughly in proportion to the severity of dyspnoea and may be less than 25 per cent of normal

RISE OF VENOUS PRESSURE

It has been shown by Harrison and others⁵¹ that rise of venous pressure artificially induced in animals (*e.g.* by intravenous infusion or by inflation of a balloon within the right auricle), immediately provokes "hyper-ventilation" (or dyspnoea), unless the vagi nerves have been previously severed. In this reflex stimulation of respiration from rise of systemic venous pressure (the "Harrison reflex"), the vagus constitutes the afferent pathway whilst the efferent "focus" is probably the heart or the great veins near the heart.

THE CAROTID SINUS REFLEX OR THE ANOXAEMIA REFLEX OF HEYMANS

Recent work suggests that, in cardiac cases, anoxaemia (deficiency of oxygen in the blood or increase of carbon-dioxide content) may induce dyspnoea through the intermediation of the "sensitive zones" of the carotid sinus and the root of the aorta. From these zones, the respiratory centre is reflexly stimulated.

Heymans⁴² was able to induce hyperpnoea in animals by perfusing the carotid sinus with blood containing less oxygen or more carbon dioxide. Further support has been lent to this theory by the experiments of Selladurai and Wright.¹⁰⁷

LOCAL MUSCLES REFLEXES

The masterly work of Harrison and his associates⁵¹ has served to focus our attention on the importance of "muscle reflexes" in the initiation of "exertional dyspnoea."

They proved by experiments on man and animals that the increased respiration of exercise is of "nervous" and not of "chemical origin." They made the test-subject open and close his hands at a rapid rate for one to two minutes, whilst the respiration was recorded by means of a spirometer. They found that the hyperventilation more or less coincides with the onset of exercise, there being no latent period, also when blood-pressure cuffs are inflated round both the arms to pressures of 200 mm (in order completely to occlude the incoming and outgoing circulation of the exercising muscles) the hyperventilation still occurs. In other words, the increased respiration of exercise is of "nervous origin."

Krogh and Lindhard⁷³ had previously concluded that the hyperventilation of exercise is due to "irradiation of impulses from the higher centres to the respiratory centre" (*i.e.* "cortical origin"). This theory was disproved by Harrison and his colleagues⁵¹ in the following ingenious fashion: (1) Harrison found passive movements of an extremity just as effective in inducing hyperventilation as active movements. (2) The hyperventilation response could be obtained with passive movements even in anaesthetized animals. They were, therefore, led to the conclusion that "increase in ventilation" from exercise is "due to a reflex arising in the moving muscles and affecting the respiratory centre."

OXYGEN-LACK OR ANOXAEMIA

There is no doubt that in a certain percentage of cases of cardiac dyspnoea, one finds definite evidence of arterial anoxaemia or reduction in the arterial "oxygen saturation." The percentage incidence of demonstrable anoxaemia in cardiac dyspnoea has varied very widely in

different statistics viz 77 per cent in Harrop's series,⁶⁴ 100 per cent in Barach and Woodwell's series,³ 77 per cent in Kroetz' series, 12.5 per cent in Fraser's series⁴¹ and 0 per cent in Cullen and Harrison's series^{20, 21} These widely divergent results are probably dependent on the type of clinical material selected for investigation

Usually, the degree of "arterial oxygen unsaturation" in cardiac dyspnoea is of a very minor order, there are cases where arterial oxygen saturation figures of 75 to 85 per cent and even 50 per cent (in very rare and fatal cases) have been recorded

That arterial anoxaemia is *not* an essential requirement in the production of cardiac dyspnoea is proved by the following facts (1) In the great majority of cases of cardiac dyspnoea, the arterial oxygen saturation figures are within normal limits, (2) When right-sided failure supervenes on left-sided, the dyspnoea shows amelioration, even when the oxygen saturation of arterial blood shows a "drop"⁴⁰ Although arterial anoxaemia may not be essential to cardiac dyspnoea, it is, nevertheless, an important subsidiary factor in a certain percentage of cases, this is particularly true for those cases of cardiac dyspnoea, who experience great relief from inhalation of oxygen mixtures. It is in cases of cardiac failure with emphysema and in long-standing cases of failure with pulmonary changes that arterial anoxaemia plays an important role in the genesis of dyspnoea

The actual mechanism concerned in the production of dyspnoea by arterial anoxaemia remains sub-judice. According to Gessell,⁴⁴ anoxaemia, by leading to "fixation" of acid ketabolites (including lactic acid) in the respiratory centres, induces their stimulation with resultant hyperventilation (Gesell's theory). On the other hand, Heymans,⁴⁰ Selladurai and Wright¹⁰⁷ are of the opinion that anoxaemia leads to stimulation of certain "sensitive zones" in the carotid sinus and at the root of the aorta, which in turn stimulates the respiratory centre, through the intermediation of a vagal reflex (the "Carotid Sinus theory")

According to Kroetz,⁴⁰ it is not the "oxygen saturation" but the "oxygen pressure" of blood that really determines the presence or absence of anoxaemia or oxygen-lack. In his opinion, definite oxygen-lack may arise with normal values for oxygen-saturation provided the "oxygen-pressure" happens to be low. In some cases of dyspnoea with normal arterial oxygen saturation figures Kroetz has demonstrated low figures for oxygen pressure, viz 55 and 65 mm Hg. This interesting theory awaits confirmation

(To be continued)

SPRUE

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

by
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The discovery of folic acid (*Lactobacillus casei* factor) has drawn more attention to the clinical picture of sprue. This symptom complex has been recognized as a distinct clinical entity since the publications of Manson from China and van der Burg from the Dutch East Indies in 1880. Although sprue was first considered to be a tropical disease, a gradually increasing number of reports of a similar condition found in the temperate zone—so-called nontropical sprue occurring in patients who have never been in endemic areas—shows that sprue is not restricted entirely to the tropics. Because of the discovery of folic acid, more attention will be paid to the diagnosis of sprue.

The diagnosis is usually easy when the disease is in its advanced stage and presents a well-defined, characteristic and unmistakable symptom complex. Even in advanced cases, however, diagnosis may be difficult because symptoms of other deficiencies are superimposed and confuse the clinical picture. Far greater difficulty is experienced when the disease is in its early stage. Its gradual and insidious beginning, its remittent course, its sharing of the symptoms with other diseases and lack of trustworthy test characteristic only of sprue, make the diagnosis difficult. As there is not one single symptom characteristic of sprue alone, the diagnosis can be made only by a combination of the course of disease and evaluation of the various symptoms and laboratory findings. In a number of cases dietary treatment and especially therapy with liver extract and folic acid are followed by such a dramatic and complete recovery that a diagnosis of sprue is indicated. But though the provisional diagnosis can be confirmed by the results of specific therapy, the diagnosis usually must be made from the clinical picture and the result of laboratory tests. It is of vital importance to recognize sprue in its early stages and to unmask it as a primary disturbance in multiple deficiencies because we are able today to treat many cases successfully and to cure a large percentage, provided therapy is started before permanent tissue damage has occurred.

SYMPTOMS

Fatty diarrhea, accompanied by meteorism and followed by emaciation, with remissions and acute relapses varying in intensity, must be regarded as the main and primary symptom. Stomatoglossitis, hypochromic and hyperchromic anaemia are frequently encountered. There also occur symptoms of deficiencies of vitamins A, B₁, B₂, C, D, K and of such minerals as calcium and phosphorus.

Steatorrhea The most striking and important of all the features of sprue is steatorrhea, usually accompanied by a diarrhea. Sometimes, although fortunately not often, constipation is present and distracts attention from the importance of a stool test. The presence of an increased quantity of fat in the stool, especially of fatty acids and soaps,

is indispensable for the diagnosis of sprue. Special caution must be observed in the interpretation of the stool test. At the very outset of the disease, or during a remission, fecal fat may be only slightly increased. As sprue often develops following chronic diarrhea and begins gradually, it is not possible to say precisely at what point the preliminary diarrhea ends and when sprue itself sets in. Therefore, in dubious cases it is advisable to repeat the stool test at regular intervals. Furthermore, it must be remembered that the food of the patient must contain a certain quantity of fat in order to ascertain by examination of the stool, the degree of failure in the process of fat splitting and assimilation. One must remember also that treatment with liver extract and perhaps also with folic acid may bring about an improvement or even disappearance of steatorrhea. Liver extract seems to contain a specific "antisprue factor" regulating fat absorption, possibly in connection with the adrenal cortex hormone. The work on folic acid seems to show that this factor corrects impaired fat absorption in sprue and therefore may be considered the true "antisprue factor."

The normal fat content of the stool in healthy persons amounts to 5 or 10 per cent of the dry weight, although some authors regard as pathologic only a fat content above 20 or even 28 per cent. This stool fat derives not from unabsorbed food fat but from desquamated epithelial cells, intestinal bacteria and intestinal secretion. The daily fat evacuation in normal individuals is about 10 or 12 Gm. in 24 hours. In sprue the total fat output in 24 hours varies between 40 and 50 per cent of the dried matter and may go up to 70 or even 80 per cent. The total quantity of fat in sprue stools may amount to as much as 80 Gm. per day. A simple microscopic test is generally sufficient to demonstrate an increase of neutral fat or split fat products.

An increased fat output is known to occur in other pathologic conditions and, therefore, cannot be regarded as of decisive diagnostic significance. Pancreatic lesions (carcinoma, chronic pancreatitis and obstruction of the ampulla of Vater) may bring about the elimination of large amounts of fat in the stools. The general clinical picture of sprue and such pancreatic disturbances may present features very much alike (chronicity, marked emaciation and debility, meteorism, hypochromic anemia and steatorrhea), but laboratory tests will lead to an exact diagnosis. The differentiation lies in the composition of the excess fat in the stools. In pancreatic fatty diarrhea the increased fat output is due to failure to split fat and the fat is, therefore, largely neutral fat. Such stools are iridescent or white or pale in colour and very often, on cooling, show the neutral fat as an oily substance or in solidified masses. Stools in sprue, though sometimes showing a similar colour, are usually frothy, more liquid and do not manifest the presence of visible neutral fat. The increased fat in the stool in sprue is largely in the forms of fatty acids and soaps. In contrast to pancreatic lesions the neutral fat of the food is split in a normal way, but the split products are not absorbed. The ratio of neutral fat to split fat falls as low as 1:18 against 1:2 in the stool of normal individuals. This increase of split fat is due to impaired fat assimilation as the result of a dysfunction of the intestinal mucosa after previous intestinal infections, with subsequent poor absorption of the "antisprue factor" which regulates fat assimilation. In cases

in which patients have been living on an inadequate diet, failure of fat absorption may be due to a true nutritional deficiency

Failure of fat absorption in association with formed and diarrheal stools, as an isolated symptom, is not uncommon in the tropics. In most of the cases the deficient fat absorption lasts for a relatively short time, disappears entirely or shows relapses. Other cases gradually develop chronic diarrhea, meteorism, fatigue, loss of weight, stomatoglossitis and hypo-ol hyperchromic anemia—in other words the unmistakable picture of sprue. *Therefore, in cases of chronic diarrhea the test of the stool for steatorrhea should never be neglected.* It seems fair to assume that this failure of fat assimilation represents one of the earliest symptoms of sprue and corresponds to the so-called pre-sprue condition.

Apart from the different nature of the fatty stools in pancreatic lesions and sprue, there are other symptoms and tests that easily differentiate the two conditions. Whereas in pancreatic diseases the pancreatic juice generally fails to enter the intestine, in sprue there is no change in the amount of pancreatic enzymes in the duodenal content. For this reason fatty diarrhea of pancreatic origin gives stools which contain a large number of undigested muscle fibres, whereas in sprue azotorrhea is seen more seldom and never to the same extent. Another finding in the stool, strongly suggestive of a pancreas lesion but usually absent in sprue, is the imperfect digestion of carbohydrate. A high diastase content in blood and urine favors the diagnosis of a pancreatic lesion, in sprue there is no increase of pancreatic enzymes, either in the blood or in the urine. Hyperglycemia and glycosuria may occur in pancreatic disturbances if the islands of Langerhans are affected, in sprue a low blood sugar curve after glucose ingestion has been found to be a fairly constant feature as well as a low blood fat curve after fat ingestion. An increased rate of basal metabolism should be interpreted as a symptom of sprue. Development of jaundice clarifies the situation in favour of a pancreatic lesion.

Much greater difficulty in differential diagnosis is encountered in the group of diseases which show defective fat absorption rather than failure of fat splitting. Involvement of the mesenteric lymph system (tuberculosis, malignancy and amyloidosis) may produce stools having a very close resemblance to the stools of sprue. Abdominal tuberculosis may affect and obstruct the mesenteric glands and main lymphatic ducts with the result that fat already absorbed cannot be carried off through the lymph vessels. This mechanical obstruction results in congestion and subsequent failure of assimilation of the split fat. Further symptoms of such a tuberculous condition resembling sprue are marked emaciation, debility, distension of the abdomen, meteorism, hypochromic anemia and abdominal distress. However, there may be other symptoms to distinguish the two diseases. The past history of the patient usually reveals previous tuberculous manifestations, or an active tuberculous process elsewhere may be demonstrable. Fever, leukocytosis, a shift to the left of the neutrophils and a high rate of blood sedimentation are suggestive of tuberculosis, whereas leukopenia, a relative lymphocytosis and normal sedimentation rate are characteristic of sprue. Ascites or palpable abdominal masses are unmistakable manifestations ruling out sprue. Hyperchromic anemia glossitis, low blood sugar curve and high metabolic rate are indicative of sprue.

The same conditions as those in tuberculosis are found if the mesenteric lymph system is involved by malignant tumors or amyloidosis. However, in these cases it generally will be possible to diagnose the primary disturbance as the mesenteric lymph system is not involved until the primary lesion—either neoplastic or of the chronic infective type—has advanced to such a degree that it cannot be missed on careful examination.

A symptom complex, with fatty diarrhea similar to that of sprue and various other sprue symptoms such as stomatoglossitis, anemia and emaciation, can be seen in patients on whom gastro-intestinal operations have been performed. In these cases either most of the small intestine has been removed or, after gastro-enterostomy, a gastro-jejuno-colic fistula has developed leading to a short circuiting of the intestine. Most authors differentiate this clinical picture from actual sprue, but in essentials it is identical. For, though in sprue the "antisprue factor" is missing in the diet or cannot be absorbed because of a functional disturbance of the intestinal epithelium, in these surgical cases short-circuiting or removal has put the small intestine out of function, thus leading to poor absorption of the "antisprue factor" and resulting in the sprue symptom.

Stomatoglossitis Besides the leading sprue symptom, fatty diarrhea, the other manifestations such as glossitis, anemia of hypochromic and hyperchromic nature, and edema are frequently to be observed. Although stomatoglossitis is generally regarded as a cardinal sprue symptom, it seems questionable whether we have the right to consider it a primary manifestation of sprue. The same oral changes are also met in pellagra, pernicious anemia and ariboflavinosis. At the beginning of the disease inflammatory changes are seen, especially at the tip and along the edges of the tongue. Eventually, the tongue becomes atrophic and looks varnished. The oral cavity may likewise be affected. Cases in which stomatoglossitis precedes the development of the classical sprue picture by months or years are classified by Manson-Bahr as "tongue or mouth sprue." However, such an isolated stomatoglossitis is generally curable by nicotinic acid or riboflavin. The fact that glossitis in sprue is cured by liver extract can easily be explained by the nicotinic acid, riboflavin and folic acid content of some liver extracts. In some cases, steatorrhea, anemia and the other symptoms of sprue may improve considerably without the tongue showing any improvement at all, or, even after a successful treatment, stomatitis may recur as an isolated morbid manifestation. We must assume that stomatoglossitis in sprue is a secondary symptom and that an isolated deficiency of one or the other factor of the vitamin B₂ group (riboflavin, nicotinic acid or folic acid) may remain or recur due to an impaired absorptive power of the small intestine.

Hyperchromic Anemia The question of the significance of hyperchromic anemia as a symptom of sprue has raised lively discussion in the literature of the disease. As a matter of fact, the anemia of sprue in many advanced cases offers a picture almost indistinguishable from that in Addisonian pernicious anemia. Blood tests in either disease reveal hyperchromic macrocytic anemia with a color index above 1, leukopenia and relative lymphocytosis. The Price-Jones curve of the red blood cells and the findings of sternal puncture

in sprue correspond to those in pernicious anemia. The identity of both forms of anemia seems to be possible, especially as either reacts to liver and folic acid therapy with a similar reticulocyte response and striking improvement of the red blood cell picture.

Of further similar symptoms, sore tongue and mouth and subacute combined degeneration of the cord have to be mentioned, although the latter is seen less often in sprue than in Addisonian anemia. Histamine refractory achylia can also be demonstrated, but in sprue it does not constitute as constant a symptom as in pernicious anemia. The similarity of the picture is sometimes so striking that, because of the hematologic findings, the two diseases were at one time declared identical by Castle and Rhoads.

If, however, one has seen a great number of patients with sprue and has kept them under close observation for many years, one comes to the conclusion that the two conditions cannot be identical, although the resultant anemia may be almost the same. There are certain differences, even hematologically, though nowadays the interpretation of the blood picture may be difficult as most sprue patients have had some liver or folic acid treatment before an exact diagnosis is made. In sprue, normoblasts are seen less often than in primary Addisonian anemia and megaloblasts can rarely be demonstrated. In the initial stage of sprue there is mostly a hypochromic microcytic anemia which is due to iron deficiency. It changes to a hyperchromic macrocytic anemia with the progress of the disease. A reversal from hyperchromic anemia to the hypochromic form is also met with, even in the same individual. Addisonian anemia only improves after administration of the intrinsic factor in the form of stomach preparations, liver extract or folic acid, whereas in sprue improvement of the red blood cells and hemoglobin can be obtained by other means. If in sprue dietary treatment succeeds in checking diarrhea and steatorrhea, an improvement of the red blood picture may take place, pernicious anemia never reacts to dietary treatment. Once the diagnosis of Addisonian anemia is established, treatment is necessary for the patient's life as permanent cure of the disease is unknown. In sprue erythropoiesis becomes and remains normal when the disease is cured, although anemia may recur in the event of a relapse of the intestinal symptoms.

Besides these differences, there are other laboratory findings distinguishing the two diseases from each other. In Addisonian anemia, owing to destruction of red blood cells, the bilirubin content of the blood is increased, and both stools and urine show an increase of urobilin and urobilinogen. In cases of sprue the blood, stool and urine tests are negative. The flat glucose tolerance curve and the low blood fat curve after fat ingestion, often encountered in sprue, cannot be demonstrated in pernicious anemia. A decrease in calcium, phosphorus and various vitamins in the blood occurs in advanced cases of sprue but not in pernicious anemia. Diarrhea may be seen in Addisonian anemia as the result of gastric achylia, but the stool never shows an increased fat content. The combination of hyperchromic anemia and failure of fat absorption points almost infallibly to a diagnosis of sprue. Difficulties in diagnosis may arise in cases where steatorrhea is not combined with diarrhea. An erroneous diagnosis of pernicious anemia may then be made because the stool test has been neglected. It seems

very probable that the few published cases of Addisonian anemia with free acidity in the stomach juice were really suffering from sprue. In all cases of suspected pernicious anemia the examination of the stool for split fats should be as much an obligatory test as the examination of the stomach juice. The demonstration of free acidity in the stomach juice and the presence of an increased quantity of split fat in the stool rules out primary Addisonian anemia and is strongly suggestive of sprue. The function of the gastric mucosa may show a marked difference in its reaction to therapy. Histamine refractory achylia is a permanent symptom in pernicious anemia, even in spite of successful therapy. In sprue when achylia is encountered the function of the mucosa of the stomach may become normal again with the improvement of the disease.

There are other general symptoms indicating that the two conditions are not identical. Patients with Addisonian anemia are pale or show a characteristic lemon-yellow tint or a distinct subicteric change of the skin or sclera, whereas the skin of sprue patients is pale-grayish, yellowish-brown or muddy in color. The emaciation and the intense weakness, so characteristic of sprue, are not observed in Addisonian anemia to nearly so marked a degree in cases with comparable blood counts, and the distended abdomen and the distressing meteorism are not encountered at all.

A question arises as to which pathologic condition in sprue causes the disturbance of erythropoiesis. The most likely explanation is that, due to the fermentation in the small intestine and its impaired absorptive power folic acid is destroyed or not absorbed. Subsequently, as a secondary symptom a condition develops similar to Addisonian anemia. Such a conception would explain why improvement of the intestinal symptoms in cases of sprue is followed by normal blood formation, even without any medication. If folic acid is given therapeutically, enough of it is absorbed to insure normal blood formation. It is of interest to note that recently Spies and his associates proposed a hypothesis that the pathogenesis of macrocytic anemia of sprue differs from that of Addisonian anemia.

Edema Among the secondary manifestations occurring in sprue edema should be mentioned. These swellings are not of cardiac or renal origin. There is no cyanosis, dyspnea or albuminuria. No improvement is seen after rest in bed or administration of digitalis. The edema may be transitory or remain for some time, even after the other sprue symptoms have been brought under control. Sometimes it develops after these symptoms have already shown marked improvement. This edema represents a secondary deficiency symptom the nature of which is not yet clear.

Multiple Deficiency Besides the symptoms already mentioned, various others may occasionally develop simultaneously and present an apparent picture of a complex deficiency state. Nearly all known vitamins and various minerals have been reported as decreased in the blood of patients with sprue. Symptoms of scurvy, arboflavinosis, deficiency in vitamins A, B₁, B₂, D, K, and in calcium and phosphorus have been noted, either singly or in combination. Sprue then may present the most complex and polymorphous of all deficiency states and sometimes the secondary symptoms are in the foreground of the clinical

picture to such an extent that the primary symptoms of sprue are overshadowed. These secondary manifestations may sometimes be due to dietary inadequacy but mostly develop when the intestinal dysfunction produces a faulty absorption of other essential factors than the "antisprue factor." It is for this reason that, in spite of a normal diet which may be even rich in vitamins, deficiency of various factors may occur. In cases of multiple deficiency one should always think of sprue as a possible underlying primary disturbance. Bennett, Hunter and Vaughan have characterized the paradoxical condition of such patients in the apt words "they are starving in the midst of plenty."

DISEASES RESEMBLING SPRUE

Pellagra The picture of pellagra may seem very similar to the symptom complex of sprue. In either disease, glossitis, diarrhea, anemia, progressive weakness, pigmentations and psychosis are to be seen. However, there is no increased fat output in pellagra. Hypochromic anemia is seen in either condition, hyperchromic anemia generally only in sprue. Dermatitis, especially of symmetrical nature is suggestive of pellagra, in sprue pigmentation of the skin may be noted, clearing up with the improvement of the disease and recurring with its return. Severe psychosis or dementia must be rated as signs of pellagra although in sprue irritability and depression are quite frequent. Differential diagnosis is difficult in border-line cases which are by far more frequent than is generally assumed.

Addison's disease Another disease with a certain similarity to sprue is Addison's disease. Both conditions are associated with vomiting, diarrhea, extreme weakness, marked loss of weight, pigmentations, apathy, depression, anemia and hypotony. In recent years there have been increasing reports of patients with Addison's disease who show an impaired fat assimilation similar to sprue. Such a steatorrhea in Addison's disease would be in accordance with Verzar's theory that the hormone of the adrenal cortex regulates fat metabolism. In such cases the diagnosis may be extremely difficult. Hyperchromic anemia must be regarded as a symptom of sprue, in Addison's disease polycythemia may occasionally be seen due to a decrease in the blood volume and hemo-concentration. Pigmentation in Addison's disease is seen in the skin and mucous membrane, in sprue, pigmentation of the skin is sometimes seen, but never in the mucous membrane. In dubious cases blood and urine tests will solve diagnostic difficulties. In Addison's disease an increase in the blood urea and a decrease in the sodium content of the blood are of diagnostic importance, also, an increase in sodium chloride and creatinine in the urine. In advanced sprue, as the result of a faulty absorption of protein, hypoproteinemia, a low calcium and phosphorus content of the blood and an increase in the indican in blood and urine are found.

Tuberculosis or Malignancy of the Intestines Finally there are some conspicuous points of resemblance between the clinical features of sprue and tuberculosis or malignant tumors of the intestines. As in sprue, indigestion, meteorism, debility, chronic diarrhea, emaciation, hypochromic anemia and edema may be seen in these conditions. However, the stool tests do not reveal steatorrhea unless the mesenteric lymph system is involved. A marked difference in the appetite can be

noted In the majority of cases of sprue appetite is normal or even ravenous, in tuberculosis or malignancy anorexia is usually present Hyperchromic anemia and, generally, glossitis are absent in tuberculosis and malignancy Sprue is not associated with fever, leukocytosis, an increase in the polymorphonuclears and a shift to the left of the neutrophils Other points of difference have been mentioned above The x-ray examination in sprue reveals an accumulation of barium in dilated coils of the intestines, a coarse mucosal pattern and a slow progress of the opaque meal In difficult cases, x-ray examination of the intestines and the presence of tubercle bacilli in the stool will help clarify the diagnosis

SUMMARY

The main and primary symptom of sprue is steatorrhea due to impaired absorption of the split fat products Steatorrhea in pancreatic lesions is the result of deficient splitting of fat Other symptoms in which the two conditions differ have been discussed

Defective fat absorption similar to that in sprue is seen when the mesenteric lymph system is involved by tuberculosis, malignancy or amyloidosis, but in such cases there are other symptoms present to differentiate them from sprue

Steatorrhea, with a symptom complex similar to sprue, occurs after gastro-intestinal operations with short-circuiting of the small intestine and must be regarded as identical to that occurring with sprue

Stomatoglossitis, hypo- and hyperchromic anemia and edema are common secondary manifestations of sprue

Stomatoglossitis is attributed to a deficient absorption of one or another of the fractions of the vitamin B complex, nicotinic acid, riboflavin and folic acid Hyperchromic anemia in sprue differs from that of pernicious anemia in regard to its pathogenesis, their differential diagnosis is discussed Edema presents deficiency state

The difficulty of diagnosis in cases of sprue with manifestations of a multiple deficiency is stressed

The similarity of pellagra, Addison's disease and tuberculosis or malignancy of the intestines to sprue and their differential diagnosis are discussed (*American Practitioner, Dec. 1947*)

Critical Notes and Abstracts

STREPTOMYCIN IN TREATMENT OF VARIOUS TUBERCULOUS CONDITIONS

Tucker presents a report on the use of streptomycin in tuberculous conditions in the Minneapolis Veterans Administration Hospital. This hospital was approved as one of the Study Units by a Committee on Streptomycin in the Central Office of the Veterans Administration for a streptomycin investigative program. Among the various tuberculous conditions to be studied were pulmonary tuberculosis, tracheo-bronchial and laryngeal tuberculosis, tuberculous sinuses and fistulae, tuberculosis of the alimentary tract, tuberculous lymphadenitis, tuberculosis of bone, joint and cartilage, genito-urinary tuberculosis, military and meningeal tuberculosis and others. Streptomycin therapy was completed in 112 cases, exclusive of therapy given in surgical cases as prophylaxis. The author summarizes his report as follows:

1 In Minneapolis, as in the larger joint investigative program, streptomycin has been found to be an effective form of therapy in supplementing other standard forms of treatment in various tuberculous conditions. In tuberculous sinuses and fistulae, in tuberculosis of the alimentary tract, in laryngeal and tracheo-bronchial tuberculosis, and in tuberculous lymphadenitis, streptomycin therapy is associated with improvement and/or healing of the local tuberculous lesion in between 85 percent and 90 percent of the cases treated. In other tuberculous conditions such as pulmonary, genito-urinary (especially renal), and the rarer medical forms of tuberculosis, streptomycin therapy is less effective, being associated with improvement in between 60 percent and 80 percent of the cases treated. Streptomycin is still less effective in producing healing or improvement in tuberculosis of bone, joint and cartilage, and in military and meningeal tuberculosis (80 percent to 45 percent improvement), but in the latter conditions achieves results so superior to other forms of therapy that its effect must be regarded as phenomenal. Streptomycin employed prophylactically in patients undergoing thoracic surgery appears to have some suppressive effect on the incidence of post-operative spreads, a marked effect in the case of pneumonectomy and lobectomy, less so in the case of thoracoplasty.

2 Various dosage regimens have been employed and their results studied. *A daily dose of one gram appears to be as effective as larger doses earlier employed (1.8 and 2.0 gms per day). Injection in two doses a day appears to be as effective as in five or six doses a day.* Some evidence has been presented that cases treated for only 60 days have as favorable an outcome as those treated for periods up to 120 days. Regimens employing still smaller doses (0.5 gm per day or less), and for shorter periods (60 days, and less) are being tested.

3 The incidence of toxicity has been appreciably reduced with the demonstration that daily doses not larger than one gram are efficacious. Vertigo and evidence of vestibular damages are one-fifth as frequent on one gram a day as with two grams a day. It is possible that toxic manifestations will be still less frequent on regimens under present study, but they remain sufficiently prominent to require careful laboratory and clinical observation whenever streptomycin therapy is used in tuberculosis.

4 On all of the dosage regimens so far employed, the development of resistance to streptomycin, on the part of the patients' tubercle bacilli, to concentrations of streptomycin above levels therapeutically possible, is an alarming observation. The greatest rate of development seems to be after about 45 days of treatment, but may be somewhat earlier. There is strongly suggestive evidence that streptomycin therapy continued after such bacterial resistance to the antibiotic has developed is associated with no further benefit at best, or with a progressive course of the disease at its worst. Further, if the phenomenon of resistance to streptomycin is an irreversible one, as most evidence suggests, once such resistance has developed it is not possible to employ the drug with benefit after its development, for possible future even greater need. The need for a regimen which will combine clinical effectiveness, a low rate of toxicity, and avoidance of the development of resistance, is acute. Such a regimen has not as yet been developed, although investigation of possibilities continues. Until it has been, it is necessary that the medical profession employ streptomycin in the treatment of tuberculosis with caution and reserve.

(Tucker, William B., Minneapolis Veterans Administration Hospital, Minneapolis Minn., *The Journal-Lancet* 68 282-292, July, 1948)

FAT IN NUTRITION

Eckstein presents one of a series of articles on nutrition which will appear later in book form as *The Handbook of Nutrition of the American Medical Association's Council on Foods and Nutrition*. It is stated that man through his evolutionary changes has developed into an animal whose gastrointestinal tract has been modified to such a state that considerable portion of fat is desirable in his diet. The bulk of the diet can be significantly decreased by the incorporation of additional fat because this foodstuff supplies more than twice the number of calories available from equivalent amounts of protein or carbohydrate.

In summarizing his report the author states that the incorporation of suitable amounts of fat (triglycerides) in the diet increases the "staying power" of the ration and the substitution of fat for carbohydrate decreases fermentation in the gut. Triglycerides of plant and animal fats are equally well digested and absorbed provided that liquefaction of these occurs in the small intestine. Plant sterols are not absorbed to any significant extent by man, while cholesterol, the chief sterol of higher animals, is well utilized. Depot fats consist primarily of triglycerides. In contrast, cholesterol, the phospholipids and the cerebroside occur in predominating amounts in the actively functioning organs of animals. Pancreatic lipase and the bile salt are the chief factors in the digestion and absorption of triglycerides from the intestine.

Cholin-containing phospholipids are intimately associated with the transport of fat acids in the body. These acids may be incorporated in the complex lipids, deposited in the fat depots, converted to other fat acids, excreted into the gut, utilized in the formation of milk fat or oxidized to carbon dioxide and water with the liberation of energy. While the majority of the fat acids are apparently exogenous in origin. Either one of the latter two is an essential constituent in the diet of the white rat and may be required by man.

Degradation of fat acids takes place in two stages. The first phase, occurring almost exclusively in the liver, consists in the production of the ketone bodies, which are disposed of in the final state in the extrahepatic tissues (notably in the kidneys and muscles). With the exception of those of low molecular weight (C_4 to C_{10} inclusive) the fat acids of milk fat originate from the triglycerides of the blood. The composition of milk fat can be altered by dietary management. The controversy on the comparative nutritive value of butter and the margarines still exists. Cholesterol, the phospholipids and the cerebrosides can be synthesized by the animal organism. Increased deposition of these occurs in the actively functioning organs in the types of lipidoses.

(Eckstein, H. C., University of Michigan, Ann Arbor, Mich., *The Journal A. M. A.* 187: 1220-1220 July, 1948.)

ENTERIC COLIC

The problem of enteric colic is considered by Brackett from the point of view of indicating causes, both physiological and mechanical, and also from the point of view of the psychological effect of habits engendered by pain and discomfort on both the child and parents. The author summarizes his report by stating that the exciting cause of colic seems to be the excessive volume of contents in the terminal ileum. The discomfort of the average typical case of enteric colic begins after the early morning feeding. It increases in intensity as the day progresses, until, from four to six p.m., the extra-ileal nervous mechanism goes into action, increasing the force of the peristaltic contractions and the intensity of the pain. The accumulated contents are gradually driven through the sphincter with a decrease in discomfort and pain.

The group of cases called by the laity "cross," "cranky," "irritable," "gassy" and ignored by the profession or called by them "neuropathic" or "having an autonomic imbalance" yield to the same treatment as do typical cases of hypercontractility of the ileum and should be so classified. The suggestion is made that the function of the sphincter in delaying the chyme is overdone and the function whereby the chyme is passed into the cecum is not free enough. In certain cases a congenitally tight sphincter, possibly hereditary, may be the cause of the colic. Further study is called for to determine how often the colic is due to intestinal allergy and how best to recognize these cases. Also, a study should be made to determine, if possible, the effect on the psychology of the baby when pain is the dominant sensation of the early weeks.

We do not know enough about the anatomy and physiology of the digestive tract of the normal child under four months, still less about the colicky infant. Cases of enteric colic are much more numerous and serious than is generally recognized. Its treatment is pitifully inadequate, resulting in a tremendous amount of pain on the part of the babies and helpless worry on the part of the parents.

(Brackett, Arthur S., Consultant, Bristol General Hospital, Bristol, Conn., *Yale Journal of Biology and Medicine* 20: 558-560 July, 1948.)

STUDIES ON PATIENTS WITH CIRRHOSIS OF THE LIVER

Stueck et al state that it is generally agreed that the concentration and nature of fatty acids in the liver vary greatly in health and disease. Changes are most marked when the liver itself is the site of the pathologic disorder. Because of its importance in the metabolism of lipids, any disease of the liver will inevitably affect the pattern of the plasma lipids. During the past few years the authors have determined the plasma and liver lipids in 21 subjects, 19 of whom had cirrhosis of the liver. All of the subjects were adults and nine were females.

Of the 19 patients with cirrhosis, 16 had ascites and 15 were jaundiced. The liver samples were obtained at postmortem. The time interval between the blood and liver samples varied from 24 hours to 254 days. The values for the various lipid fractions over these periods of time were altered significantly in only one case. None of the patients improved clinically to any significant extent during the period of observation. The most consistent and outstanding change in the plasmas in all of the patients with cirrhosis of the liver was the alteration of the ratio of free to total cholesterol which was inverted in every instance. Plasma lipids were elevated in seven cases, and in three patients this was associated with marked increase in the liver lipids.

In a total of five cases liver lipids were greatly increased. In 12 patients the only significant change in lipid distribution in the plasma was in the ratio of free to total cholesterol. The percent water was determined in the livers of six patients. When lipid fractions were calculated on the basis of the dry weight of the liver, their relation to each other was unchanged. Partition of the phospholipids was done in four of the livers, and the relative concentrations of lecithin, cephalin and sphingomyelin in three of these cases were very similar to those reported by Thannhauser and showed an average percentile distribution of phospholipids of 63.3, 31.6 and 5.0 percent, respectively.

Vitamin A and carotene levels were determined in the plasmas and livers of 11 of the cases. Vitamin A levels in plasma were uniformly low and carotene was also below normal levels in most of the cases. In all but two of the livers the vitamin A and carotene levels were below normal values.

In final comment the authors state that their observations on lipid fractions in the plasmas and the livers of the same patients show that there is no absolute correlation between the amount of total fatty acids in the plasma and in the liver. Total fatty acids in the plasma may be elevated without a regularly associated increase in the concentration of fatty acids in the liver.

(Stueck, George H, Jr, Third (New York University) Medical Division, Bellevue Hospital, New York, Rubin, Saul H, Clarke, Delphine H, Graef, Irving, and Ralli, Elaine P. *The American Journal of Medicine* 5: 188-201 August, 1948.)

CHRONIC RELAPSING PANCREATITIS

Gambill et al present an analysis of 27 cases of chronic relapsing pancreatitis associated with disease of the biliary tract encountered in the years 1939 through 1948 as compared with an analysis of 29 cases of chronic relapsing pancreatitis without disease of the biliary tract encountered during the same years in an attempt to determine similarities and dissimilarities of the two series.

They found that the anatomic and histopathologic features of the disease in the pancreas are essentially the same in the two series of cases, including interstitial fibrosis, residual necrosis, cyst and abscess formation and deposition of calcium. Chronic relapsing pancreatitis in both presence and absence of biliary tract disease occurs more frequently in males than in females. Clinical features, such as primary localization of the pain in the left upper quadrant of the abdomen and extension to the left upper quadrant, left anterior part of the chest, left side of the back and left shoulder, occurred with the same frequency in both series.

Physical and laboratory findings in the two groups of cases were similar. It was further found that the same sequelae, due to involvement of the pancreas, appear regardless of the presence or absence of cholecystic disease. The most frequent sequela in both series is dilatation of the common bile duct due to pressure of the enlarged pancreas on the neighboring structures. The problems of diagnosis of chronic relapsing pancreatitis are increased when accompanied with disease of the biliary tract. Roentgenologic findings and tests of pancreatic function should lead to a correct diagnosis in a high percentage of cases. The authors state three possible relationships between cholecystitis and chronic pancreatitis: (1) Chronic pancreatitis is secondary to cholecystitis. (2) Cholecystitis may be secondary to the pancreatitis. (3) Cholecystitis and pancreatitis may occur simultaneously and could well be due to the same etiologic agent. Treatment of chronic relapsing pancreatitis associated or unassociated with disease of the biliary tract is the same, except that there is need for surgical removal of the diseased gallbladder.

(Gambili, Earl E. Division of Medicine, Mayo Clinic, Rochester, Minn., Confort, Mandred W., and Baggenstoss, Archie H., *Gastroenterology* 11: 1-83 July, 1948.)

SHOULDER PAIN AND BRACHIALGIA.—(R. Leriche — *Progres Medical, Paris*) According to Leriche cold, epidemic neuraxitis, subdeltoid calcification, a glomus or a cervical rib may be the cause of brachialgia which will be identified easily. In the absence of one of these causes two others may be considered, namely, *herniation of intervertebral disk* or *abnormality of the thoracic outlet*. Frequently the symptoms of herniated disk, such as stabbing pain or pinprick pain, heaviness, dead fingers, tingling and dysesthesia may be manifested only approximately in the area of the affected root. There may be radiating pain in the nape of the neck, in both shoulders and in the breast. The motor phenomena, hypotonia, fibrillary contractions and disturbances of reflectibility may be more closely localized. There seem to be few vasomotor disturbances associated with herniation of the disk. Attacks resembling Raynaud's syndrome may be absent, although they are common in the scalenic syndrome and in cases of cervical rib or abnormal first rib. In herniation of the disk the contact is purely radicular. In the syndromes of the subclavian cavity and of the outlet of the thorax there is contact with the subclavian, as demonstrated by the high incidence of arterial dilatation or of distant thromboses. In the latter syndromes there may be occasional cramps. In any type of brachialgia the symptoms may be bilateral. Nocturnal predominance of the pain is characteristic of the syndrome which originates in the subclavicular cavity. Compression of the vein in the

costoclavicular interval may be one of the causes. Symptomatology frequently may thus be an aid to the clinical diagnosis of brachialgia, while roentgenography will establish the diagnosis when the transverse process of the seventh cervical vertebra appears like the beak of a toucan or thinned one should consider a stellate syndrome, on the contrary when an obliterated intervertebral space may be seen in the upright column, and the closure of an intertransverse aperture in the oblique, one should consider herniation of the disk. Repeated infiltrations of the stellate ganglion or section of the scalenus should be carried out in the first case and laminectomy in the second. Section of the scalenus should not be done without additional exploration of the superior aperture of the thorax, and in certain cases it would be combined with excision of part or all of the first rib.

PLAGUE, EXPERIMENTAL, USE OF STREPTOMYCIN IN TREATMENT OF—(*S F Quain, L E Foster, A Larson and K F Meyer, Proc Soc Exper Bio & Med vol 66, pages 528-532, December 1947*)

Streptomycin in amounts of 0.4 to 4 micrograms per cubic centimeter was bactericidal in vitro for different strains of *Pasteurella pestis* in five days. In mice, advanced, experimentally induced bubonic plague was completely cured with 500 micrograms every 3 hours for 8 days, a total of 12.0 mg. In experimental septicemic plague, between 80 and 90 per cent of the mice were cured with a total of 1200 to 1800 micrograms of streptomycin administered early in infection. In experimental pneumonic plague, a total of 5 gm of streptomycin sterilized lungs and lymph nodes of mice within 100 hours after beginning treatment. On the basis of these experimental results it is suggested that human plague be treated, as soon as diagnosis is made, with daily doses of 2 Gm of streptomycin in bubonic plague, and 4 to 6 Gm in the septicemic and pneumonic types, the injections to be given every four to six hours for the first two days and at reduced dosage schedules thereafter for at least eight days.

STREPTOMYCIN IN HUMAN PLAGUE—(*P V. Karamchandani and Sunder Rao—Lancet, London, I, 1-48 (Jan 3 1948)*)

Karamchandani and Sunder Rao report that 5 patients who were practically moribund with plague were treated with intramuscular injection of streptomycin, 0.125 Gm being administered every three hours. The outbreak of plague occurred in the Anantpur district of Madras Presidency, and so far 152 cases have been observed, with 66 deaths. The five patients treated with streptomycin are all alive and well today. The streptomycin treatment was usually continued for three to four days. Most of the patients received a total of 4 Gm. of streptomycin. Improvement was usually noticeable after 1.5 Gm had been given, or after about thirty-six hours. No adjuvants were given with the streptomycin and all cases had been bacteriologically verified as plague.

LEPROSY, USE OF DIASONE IN TREATMENT OF—(*G H Faget and P T Erickson, J. Amer Med Assn vol 136, pages 451-457, Feb 14, 1948*)

The authors report: "It seems that chaulmoogra oil will gradually be abandoned as an inadequate remedy (in leprosy) and that the sulfone drugs will replace chaulmoogra oil until a better treatment is evolved."

The active principle in each of the three sulfone derivatives used appears to be diaminodiphenylsulfone, the parent chemical. Diasone is reported to have the advantage over the sulfone compound given in earlier trials, in being less toxic by oral administration. Treatment with Diasone is started with 0.8 Gm. by mouth daily. After two weeks, provided no toxic reactions occur, the dose is increased to 0.8 Gm. twice daily, and after a few more weeks, to 0.8 Gm. three times daily. Periods of two weeks without medication every two months are advised, and blood and urine examinations should be made every three weeks. Iron and liver therapy may be necessary to counteract secondary anaemia. After six months of treatment objective improvement was shown in 25 per cent of patients, after one year in 60 per cent and after three years in almost 100 per cent.

DIABETES MELLITUS, USE OF CHOLINE CHLORIDE IN TREATMENT OF—(*L. Pelner, B. Davidson, S. Waldman and R. Margolis. New York State J. Med. vol. 48, pages 523-524, March, 1, 1948*)

Not as a substitute for insulin, but because of a possible salutary effect on carbohydrate metabolism, choline supplements were added to the diet of 26 diabetic patients. In eight patients there was no response, but in 18 patients the blood sugar level fell, the patient gained weight and there was decided improvement in well-being. In some patients the results were spectacular. Response usually became evident within two weeks. In the successful cases, the dosage of insulin could be reduced and finally eliminated. Some of the patients took choline chloride for six months, but showed no ill effects. One gram of choline chloride dissolved in 1 dram of water was given four times a day. The diet consisted of 250 Gm. of carbohydrate, 95 Gm. of protein, 75 Gm. of fat (2,055 calories per day), and vitamin supplements. The authors believe that those diabetic patients with high cholesterol content in the blood are the best subjects for administration of choline. Two of the patients treated successfully had failed to respond to medication with B complex.

DIABETES, RETINOPATHY ASSOCIATED WITH, USE OF RUTIN THERAPY IN—(*L. M. Levitt, M. R. Cholst, R. S. King and M. B. Handelsman, Amer. J. Med. Sc. Vol. 215, pages 180-185, Feb. 1948*)

Twelve diabetic patients having both increased capillary fragility and retinal hemorrhages were treated with rutin, 20 mg. three times daily, for two months, then 40 mg. three times daily for another month. Two patients were given ascorbic acid, 100 mg. three times daily, for one month prior to rutin therapy. In five patients ascorbic acid was continued in the same dosage, together with rutin. All patients except one received insulin, in doses varying from 10 to 55 units. Only two patients had glycosuria during the three month period of observation. No changes were made in the diabetic regimen of any patient. Marked improvement was noted in cutaneous capillary fragility in 3 patients, moderate improvement in 1. In 2 of these improvement accompanied a reduction in hypertension. Only 5 fundi (4 patients) improved, in 2 of these, retinal hemorrhages cleared completely, without improvement in capillary fragility. In one case, diabetic retinitis progressed rapidly despite treatment.

TREATMENT OF DIABETIC COMA—(*A Marbal—Kansas Medical Society Journal, Topeka, 49 1-52 (Jan) 1948*)

Marbal shows that it is the careless patient, the patient with poorly controlled diabetes, in whom diabetic coma is most likely to develop. This indicates the importance of education of the patient and his family with regard to the disease. Patients make errors which may precipitate diabetic coma. Even well trained patients omit insulin during times of acute illness when food intake is scant. The patient, fearing hypoglycemia, reasons "If I don't eat, I should not take insulin." The result is increasing hyperglycemia with development of acidosis and eventual coma. Patients must be made to understand that in acute illness insulin must be continued, and if the illness is accompanied by fever an even greater dose of the drug may be necessary. The most treacherous pitfall in the treatment of diabetic coma is the danger of giving too little insulin, because of an unwarranted fear of hypoglycemia. As soon as the diagnosis is made, a preliminary large dose of unmodified insulin, at least 50 units and in most patients 100 units, should be given subcutaneously. A second common pitfall is the danger of not replacing adequately the fluid and electrolytes lost by diuresis and vomiting. Administration of dextrose during the first few hours of treatment is regarded by the author as another pitfall. He lists reasons why the use of dextrose parenterally during the first few hours has no place in treatment. When consciousness has been regained and an hour or two after vomiting has subsided, fluids by mouth should be begun. After preliminary trials with water, warm broths, thin gruel, tea with sugar, orange juice and ginger ale should be given at a rate of 100 to 150 cc an hour. After the initial large dose of insulin has had the desired effect, further administration of insulin may be made, at first hourly and later at two, three or four hour intervals, according to the results of the Benedict test for sugar in urine. Within eighteen to twenty-four hours, a soft solid diet may be begun and use of protamine zinc insulin started.

HIATUS HERNIA CONFUSED WITH CORONARY THROMBOSIS—(*G C Linn—New York State Journal of Medicine, New York 48 225-236 (Feb 1, 1948)*)

Linn reports 8 cases of hiatus hernia which were originally diagnosed as coronary thrombosis. These cases demonstrate that hiatus hernia may mimic angina pectoris and coronary thrombosis. The serious prognostic outlook in coronary thrombosis or angina pectoris makes it important that the true cause for thoracic pain be ascertained. The pain of hiatus hernia is probably initiated over the visceral afferent fibers that supply the esophagus and cardiac portion of the stomach or over the sensory afferent fibers from the diaphragm, contained in the phrenic, middle or lower thoracic nerves, thus, the pain is referred to the same segments as is cardiac pain. Overdistension or irritation of the herniated portion of the stomach may be responsible for the production of the anginal or coronary type of pain. It is important to remember that the angina-like pain of hiatus hernia is more apt to be associated with eating than with effort. The patient usually complains of a good deal of eructation and feels better when he is up and around.

RUTIN A THERAPY FOR THE HEMORRHAGIC COMPLICATIONS OF HYPERTENSION (*John Q Griffith, J, Proc Inst Med Chicago 16 484, Oct., 15, 1947*)

The clinical evaluation of rutin therapy has met with certain difficulties due to a number of factors (1) the lack, until recently, of suitable experimental methods for the determination of rutin activity in animals; (2) the natural hesitation to perform controlled studies with patients subject to retinal hemorrhage, apoplexy, and death, and (3) the hitherto limited supply of rutin. Brief reports are given of experimental work showing effect of rutin in opposing abnormally increased capillary permeability and fragility in guinea pigs and rats, in decreasing the blood coagulation time in the rat, and in prolonging the effect of epinephrine in isolated guinea pig intestine.

The present report concerns the clinical study of 1,600 hypertensive subjects, in addition to 79 patients half of whom were hypertensive and who were included because of recent retinal hemorrhage. Capillary fragility was measured by modification of the Gothlin technique. Capillary permeability was determined by measurement of cutaneous lymphatic flow by the patent blue method of McMaster.

Increased capillary fragility was noted in 19 per cent of the 1,600 subjects and increased capillary permeability in an additional 11 per cent. A history of apoplexy occurring within sixteen months of the period of study was obtained in 10 per cent of those showing a fault of the capillary wall, in contrast to an incidence of 1.9 per cent in the remainder, i.e. 69 per cent of patients with a history of apoplexy were within the group with a fault of the capillary wall. Nine per cent of patients with capillary wall fault gave a history of retinal hemorrhage that was confirmed by ophthalmoscopic examination, the incidence in the remainder was 2 per cent. A fault of the capillary wall was found in 73 per cent of all patients with retinal hemorrhage, including the 79 patients specifically referred because of this condition.

Rutin was administered in an initial total daily dosage of 60 mg to 189 patients with increased capillary fragility or permeability, whose response to therapy was observed for periods ranging up to forty-eight months, averaging sixteen months. Tests of the capillary integrity were made every six weeks so long as they were abnormal, and every three months after return to normal. The initial dosage was maintained when the repeated test was normal, and was increased, usually by 20 mg per day, if the test was abnormal. A daily dosage of 60 mg was sufficient for 72 per cent of patients, 80 mg or less for 87 per cent, the remainder required higher dosages, up to 400 mg daily.

In 75 per cent of these 189 patients capillary tests became normal and remained so, most of the remainder comprised uncooperative subjects in whom therapy was irregular, but a small group of 8 per cent followed therapy carefully and yet failed to improve. Apoplexy occurred in 1.5 per cent of the treated group with normal capillary tests during the sixteen month period following study, and in 9 per cent of those in whom tests remained increased or in whom treatment was irregular. The same respective incidences of retinal hemorrhage were observed as regards patients with normal and abnormal tests. However, in the 52 subjects who were followed (from the special group with previous retinal hemorrhage), further hemorrhage occurred in 44 per cent.

(5.7 per cent in those with normal tests and 88.3 per cent in those with abnormal tests)

Increased capillary fragility or permeability appears to develop in approximately 8 per cent of hypertensive persons treated with thiocyanate, and in a few instances apoplexy or retinal hemorrhage has ensued. It is the author's practice, therefore, to correct an existing fault of the capillary wall by administration of rutin before starting thiocyanate therapy. If capillary tests become abnormal again the dosage of rutin is increased, or thiocyanate is discontinued, or both. Rutin accordingly is a valuable adjunct to thiocyanate treatment of hypertensive patients when capillary fragility or permeability may be a complicating factor.

TETRAETHYL AMMONIUM BROMIDE IN HYPERTENSION—(*G W Hayward Lancet, London 1 1-48 (Jan 3, 1948)*)

This investigation by Hayward was undertaken to determine whether the administration of tetraethyl ammonium bromide would be a useful preoperative test in the selection of hypertensive patients for sympathectomy. He found that its administration to patients with essential hypertension leads to a considerable fall in blood pressure in nearly all cases. This is caused by paralysis of the autonomic ganglions with a resultant blocking of the efferent sympathetic vaso-constrictor impulses. After intravenous injection the blood pressure remains low for five to thirty minutes, and after intramuscular injection, for two to eight hours. Tetraethyl ammonium bromide is less effective than sympathectomy in producing a maximal degree of vasodilatation. Patients with hypertensive heart failure have temporary relief of orthopnea and dyspnea when the blood pressure is lowered with tetraethyl ammonium bromide. There is an increase in the vital capacity, tidal air and pulmonary ventilation per minute, with a fall in venous pressure. Pulmonary congestion is probably diminished as a result of the extensive peripheral vasodilatation. Tetraethyl ammonium bromide may be useful in the emergency treatment of acute left ventricular failure. In patients with chronic congestive failure the fall in urinary output which results from the lowering of blood pressure makes the use of tetraethyl ammonium bromide inadvisable at present.

ACTION OF TETRAETHYL AMMONIUM BROMIDE—(*A M Boyd et al Lancet, London 1 1-48 (Jan 3, 1948)*)

Boyd and his associates studied subjective phenomena and changes in pupils, blood pressure and pulse rate in 50 persons, 25 of whom served as controls. Of the other 25 patients, 15 had obliterative vascular disease with or without hypertension and 10 were subject to vasospastic episodes. The authors found that tetraethyl ammonium bromide has a limited practical value in the study of the peripheral vascular response to sympathetic block and in no way compares with such reliable and proved tests as local nerve block or paravertebral block.

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Original Contributions

ASCITIS

PRELIMINARY OBSERVATIONS ON A NEW SIGN OF ASCITIS

by

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Various signs of diagnostic import in cases of ascitis, such as the "horse-shoe shaped area of dullness", "shifting dullness", fluid thrill or "succussion wave" and the "para-umbilical zone of dullness in the genu-pectoral position," have already been discussed in elaborate detail in the medical literature of the past. With this vast array of physical signs of diagnostic value, at the disposal of the clinician, the diagnosis of ascitis has been reduced now-a-days to a minor diagnostic problem.

In view, however, of the very high incidence of ascitis cases in practice, any new sign in the realm of physical diagnosis that can serve to facilitate or confirm the diagnosis of free fluid in the abdomen, warrants our close attention and study.

Whilst clinically investigating a case of ascitis, about two months ago, I was rewarded by the accidental discovery of, what appears to be, a hitherto undescribed sign of free fluid in the abdomen. Since that time, having had the opportunity of testing this sign out in about forty cases of obvious ascitis and in forty normal controls, I have been impressed by the high incidence of "positive results" in the former group.

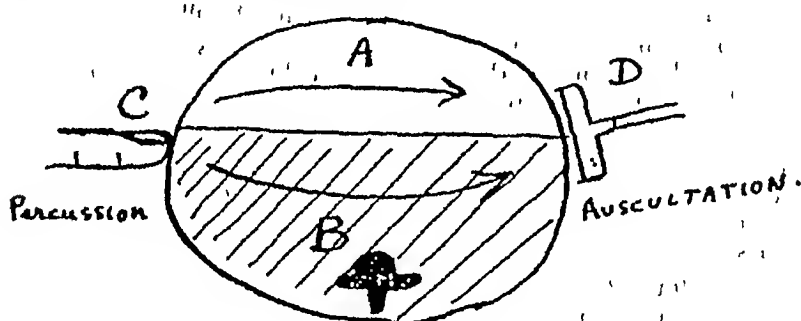
The procedure adopted for eliciting this sign has been as follows. In a suspected or proved case of ascitis, the abdomen is "flicked" or percussed (with a solitary stroke) on one flank whilst the opposite flank is carefully auscultated with a Bowles chest-piece and a binaural stethoscope, the patient being in the dorsal recumbent position with the legs partially flexed. In non-ascitis cases, it is customary to hear, during this manoeuvre, a "single sound" corresponding to the single percussion stroke applied to the opposite flank. The auscultatory sound frequently assumes a consonating or metallic character.

When the same manoeuvre is applied to cases of ascitis, with moderate or large amounts of free fluid in the abdomen, instead of one sound it is customary to hear two distinct sounds (the "double sound") to each percussion stroke. In the majority of cases, the two components of the "double sound" appear distinct (or separated from each other by a short interval of time). The quality or character of

the sounds does not appear distinctive in cases of ascitis. The two sounds may be "thudding" in character although more often they display a peculiar metallic or consonating or "echo-like" character. In a couple of cases of ascitis observed by me, whilst one of the two sounds was thudding, the other was distinctly metallic or ringing in character. The "double sound" is, as a rule, not obtained indiscriminately all over the contralateral flank (with the patient in the dorsal recumbent position) and may have to be looked for with care, in most cases, it is obtained with the greatest clarity somewhere along the upper border of dullness of the fluid.

The intensity, character, and spacing of the two sounds are variable from time to time even in the same case and appear to depend on a multiplicity of physical factors. A change-over from a "double sound" to a "single sound" or vice versa may occur in the space of a few hours in a given case.

The firm application of pressure (with the inner border of the palm) in the region of the patient's umbilicus, as employed customarily in the elicitation of the "fluid thrill" or "succussion wave", does not appear to alter the result in any way.



The factors operative in or responsible for the "double sound," in cases of ascitis, are not as yet clear. In the accompanying figure an attempt has been made to explain the possible mechanism concerned.

The percussion note at C is probably conducted at different rates through the fluid medium (B) of the ascitis fluid and through the air-filled viscus (A), thus resulting in reduplication of the sound or a double sound at D.

The above explanation is, however, purely conjectural and requires confirmation.

Incidence of "positive" in our series of cases

The result is classified as "positive" when the auscultatory finding is a "double sound" and as "negative" when it is a "single sound". The double sound may be in the nature of a "reduplicated" or "split" sound, but in the majority of "positives", there are two distinct sounds, separated by a short interval.

Out of 40 cases of ascitis (with moderate or large amount of free fluid in the abdomen) investigated by me, during the past two months, with the "percussion-auscultation technique", described herewith, as many as 25 cases (or 62.5 per cent) yielded positive results (i.e., a

"double sound"), a "single sound" being observed in only 15 cases (or 37.5 per cent).

The same technique when applied to forty normal controls (with no evidence of fluid collection in the peritoneal sac) yielded positive results or the "double sound" in only 3 cases (or 7.5 per cent) and negative results or "single sound" in as many as 37 cases (or 92.5 per cent).

In view of the much higher incidence of the "double sound" (or "positive result") in the ascitic group (being encountered over eight times more frequently in the ascitic than in the non-ascitic group), the afore-mentioned manoeuvre is recommended as a confirmatory sign in cases of ascitis. It is apparently of little or no value, in small accumulations of fluid within the peritoneal sac, when the result is usually negative. On the other hand, in those cases of ascitis where "shifting dullness" and "fluid thrill" are elicitable, the sign is frequently positive. The sign described here is, therefore, more of academic interest than of diagnostic value in cases of ascitis.

SUMMARY

A hitherto undescribed sign, (viz., "the double sound") based on a "percussion auscultation technique" is described in cases of ascitis. It appears to be a confirmatory sign of ascitis, more of academic interest than of diagnostic value. Since the present report is based on a limited number of cases only, further study will have to decide either the acceptance or rejection of this apparently new sign of ascitis.

CARDIAC DYSPNOEA

A PHYSIOLOGICAL APPROACH TO ITS PATHOGENESIS

(WITH A REVIEW OF THE MEDICAL LITERATURE)

by

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(Continued from last issue)

CARBON DIOXIDE RETENTION

In view of the universally recognized stimulant action of CO_2 on the respiratory centre, it is only natural that accumulation of CO_2 in the blood has been incriminated in the causation of cardiac dyspnoea. *Incidence of CO_2 -retention in cardiac dyspnoea* CO_2 -retention is demonstrable in a small percentage only of cases of cardiac dyspnoea. If anything, cardiac dyspnoea is more often associated with CO_2 -values below normal (i.e., below 40 to 55 Vols percentage for arterial blood) rather than with figures above normal.

O_2 -lack far more common than CO_2 -retention Carbondioxide retention in the blood is much less common than oxygen-lack or anoxaemia, as a matter of fact oxygen-lack is invariably demonstrable in cases of CO_2 -retention. In the opinion of Kroetz,⁴⁰ CO_2 retention only arises if the "Oxygen-pressure" of arterial blood falls below 40 or 45 mm Hg.

Its insignificant role in cardiac dyspnoea In view of the fact that in the great majority of cases of cardiac dyspnoea, arterial- CO_2 value are normal or below normal (rather than high), one is forced to the conclusion that retention of CO_2 in the blood plays but an insignificant role in the evolution of cardiac dyspnoea.

Cardiac cases with CO_2 -retention CO_2 -retention is more or less confined to cases of heart-failure associated with extreme degrees of pulmonary engorgement and to cases arising secondarily to chronic pulmonary diseases like emphysema and extensive pulmonary-fibrosis.⁴⁰

Modus operandi of CO_2 -retention—According to one group of workers, carbon dioxide increases the intracellular acidity of the respiratory centre by lessening or reducing the diffusion gradient between the cells and the blood and thus stimulates the respiratory centre. The recent work of Heymans⁴⁰ and of Selladurai and Wright,¹⁰⁷ however, suggests the possibility of CO_2 -action on the respiratory centre through the intermediation of the carotid sinus or a vagal reflex.

Shift of the blood p-H towards acidity—Cardiac dyspnoea has been attributed from time to time, to an acidosis or "shift of the blood-p-H towards acidity."

The insignificant role of acidosis—This has been demonstrated by Fraser, Rose and Dreyer⁴⁸ who found low figures for H-ion concentration (instead of high) in most cases of cardiac dyspnoea. It has been shown recently that in cardiac dyspnoea, the hyperventilation by washing out CO_2 from the blood actually leads to an alkalosis rather than acidosis.

Cardiac cases with acidosis—A shift of the blood p-H towards acidity is particularly demonstrable in cases of cardiac failure with severe pulmonary congestion, or lung-disease and also in the terminal stages of right-sided failure

Causes of acidosis in cardiac dyspnoea—The increased H-ion concentration in the blood in rare cases of cardiac dyspnoea, has been explained differently by different authors. It has been attributed by some to carbon-dioxide retention secondary to severe impairment of pulmonary gas-exchange, whilst others regard it as secondary to an increase in the lactic acid content of the blood, according to Meakins and Long⁸⁵, the blood lactic acid may rise from the normal of "below 25 mg per cent" to even 100 mg per cent or more in the moribund cases of heart-failure. The rise in blood-lactic acid has been attributed to (i) defective destruction of lactic acid by the liver, the latter being "congested", (ii) defective conversion into glycogen within the muscles and (iii) retention secondary to Kidney-damage

CLASSIFICATION OF CARDIAC DYSPNOEA

For convenience, the following main categories of cardiac dyspnoea are distinguished —

- (1) Exertional dyspnoea
- (2) Postural dyspnoea
 - A Orthopnoea
 - B, Trepopnoea
- (3) Nocturnal dyspnoea (Paroxysmal)
 - A Cardiac asthma, or Paroxysmal Nocturnal Dyspnoea
 - B Periodic breathing
- (4) Evening dyspnoea (of Harrison)
- (5) Continuous dyspnoea
- (6) The dyspnoea of complications (e.g. hydrothorax, pericardial effusion, ascites, pneumonia, pulm embolism, coronary thrombosis, etc)
- (7) Psychogenic dyspnoea or suspirous breathing

EXERTIONAL DYSPNOEA

Dyspnoea of effort or exertion may be physiological or pathological. Perfectly normal individuals experience shortness of breath or dyspnoea on undertaking unusually severe forms of exertion, such as climbing a hill or going up several flights of stairs. Although the dyspnoea of cardiacs (exertional) is in no way "qualitatively" different from that of normal individuals, it displays the following two contrasts from the "quantitative" standpoint viz (1) small amounts of exertion or even the normal activities of life may suffice in inducing the dyspnoea of cardiacs (2) whilst the physiological dyspnoea of normal healthy subjects is of short duration or momentary, that of cardiac cases tends to be much more persistent

Pathogenesis—In view of the apparent complexity of the matter, the causative factors or pathogenetic mechanisms of exertional cardiac dyspnoea may be considered under the following main categories viz "predisposing factor or factors" and "precipitating" or exciting factors (the so-called "trigger mechanisms")

Predisposing Factors—In the great majority of cases, the predisposing mechanism has been proved to be the factor of "pulmonary engorgement or congestion", which in turn leads to (1) a diminution in

vital capacity⁶¹ and (2) a reflex increase in ventilation⁶¹. As shown already, there results a diminution or fall of "respiratory reserve" or "respiratory factor of safety". If the pulmonary congestion is severe, the respiratory reserve sinks low enough to induce "continuous" dyspnoea. If the pulmonary congestion is mild, then the patient approaches the "dyspnoea threshold" without being actually dyspnoeic. Any further "tipping" of the scale to or beyond the "dyspnoea threshold", by any further increase of ventilation or reduction of vital capacity, induces dyspnoea. This is just the mechanism concerned in exertional dyspnoea, exercise or exertion starts off certain subsidiary mechanisms which, by further increasing an already raised "ventilation index", lead to shortness of breath. These subsidiary mechanisms of exercise come under the next heading of "precipitating factors" (See Table 1).

TABLE I
THE PHYSIOLOGICAL MECHANISM OF EXERTIONAL DYSPNOEA

Initiating or Precipitating Factors

| | | | |
|---|--|--------------------------------|--|
| 1 | Chemical Factors — | A. Low oxygen saturation | } Principal Mechanism |
| | | B. Low oxygen pressure | |
| | | C. Retention of carbon dioxide | |
| | | D. Altered p.H. of blood | |
| 2 | Diminished capacity to increased cardiac output | | |
| 3 | Local muscle reflex ⁶¹ of Harrison (vagal reflex) | | |
| 4 | Rise of venous pressure (vagal reflex) | | |
| 5 | Diminished cerebral blood flow | | |
| 6 | Fall of pressure in the carotid sinus and aorta | | |
| 7 | Cortical impulses from the cerebral cortex to the Respiratory centre | | |
| | | | (Usually stimulation of Respiratory centre) |
| | | | ↓ |
| | | | Increased Ventilation |
| | | | ↓ |
| | | | Aggravation of an already existing state of Pulmonary congestion |
| | | | ↓ |
| | | | Diminished "Respiratory Reserve" |
| | | | ↓ |
| | | | EXERTIONAL DYSPNOEA |

Precipitating Factors (or "Trigger Mechanisms")—During exertion, one or more of the following mechanisms, by coming into play, precipitate the onset of dyspnoea, (either through increased ventilation or through reduction of vital capacity) —

1. **Through Local Muscle Reflexes (Harrison's Hypothesis)**⁶¹ According to Harrison,⁶¹ this mechanism comes into play even during mild forms of physical effort. During exercise, the muscles which participate in the exercise, send forth impulses to the respiratory centre, through the intermediation of a vagal reflex, Harrison has adduced both clinical and experimental support in evidence of this theory.

2. **Alterations in the chemical composition of the blood**—The main alterations concerned are (1) decrease in the "oxygen saturation" or "oxygen pressure" of arterial blood, (2) an elevation of the CO₂ or carbon-dioxide content of the blood, and (3) an increase in the H-ion concentration of the blood. As already stressed elsewhere, these factors are of subsidiary importance and play a role only in a percentage of the more severe and prolonged instances of cardiac failure. Their role is through the intermediation either of the respiratory centre or of the carotid sinus.

3. **Diminution of cerebral blood-flow**—Any appreciable reduction in the cerebral blood flow through the medulla may result in stimulation of the respiratory centre.

4 *Rise of Venous Pressure* —Increase of general venous pressure, as in cases of right-sided cardiac failure or a *systole droite*, may induce an increase in ventilation, through the intermediation of a vagus reflex (the so-called "Harrison reflex").⁶¹

5 *Fall of arterial pressure* —Drop of arterial pressure either in the root of the aorta or in the carotid sinus may induce a reflex stimulation of the respiratory centre.

6 *Impulses from "higher centres"* —According to Krogh and Lindhard,⁷³ hyperventilation after exercise may be secondary to "irradiation of impulses from the higher centres to the respiratory centre." This is considered unlikely by Harrison.⁶¹

7 *A reduced "maximum cardiac output"* —Cases of heart-disease are said to exhibit a diminished ability to increase the cardiac output, in other words, their "maximum cardiac output" is much lower than in normal individuals. In Harrison's opinion,⁶¹ this factor only comes into operation during "moderate" exertion, in cases of "diminished cardiac reserve but without frank congestive failure."

ORTHOPNOEA

Orthopnoea may be regarded as that "form of respiratory distress that is induced or aggravated by assuming the recumbent posture." As a corollary to this definition, one may also state that an alleviation or reduction in distress follows the adoption of a "proped-up" or "sitting-up" posture, in such cases.

Pathogenesis —Innumerable theories have been propounded from time to time in order to explain the "orthostatic nature of the dyspnoea in cases of this type." Of these, the most widely discussed are the following viz —

- 1 *The Theory of Pulmonary congestion*^{40, 61} or engorgement (widely accepted)
- 2 *The Theory of "diminished cerebral blood-flow"*
- 3 *The Theory of Haldane, Meakins and Priestley*⁶⁰

Of these three hypotheses, the first being in favour at the present time, will be discussed before the others.

The Theory of Pulmonary Congestion or Engorgement —According to this theory, dyspnoea during recumbency (such as occurs in orthopnoea) is secondary to a state of increased pulmonary congestion, whilst alleviation of symptoms on adoption of the sitting-up or upright posture is permitted by diminution in this state of pulmonary engorgement.

The importance of the factor of pulmonary congestion in cases of orthopnoea, is most simply proved by the following clinical relationship viz, (1) orthopnoea is usually noted in cases of left-sided or left ventricular failure, which type of cardiac failure is distinguished by its high degree of pulmonary congestion. (2) The supervention of right ventricular failure in cases of left-sided failure results quite often in a paradoxical amelioration in the state of orthopnoea, in spite of the fact that the general condition of the patient as well as his oedema, cyanosis and hepatomegaly are much worse. The alleviation of respiratory distress in such cases, may be accounted for by the supervention of the right-sided failure which leads to a reduced degree of pulmonary congestion.

Assuming the important role of pulmonary congestion in the genesis of orthopnoea, it is necessary to analyse, at this stage, the exact relationship of the respiratory distress with the posture of the patient. Why, for instance, is this state of dyspnoea aggravated by recumbency and alleviated or relieved by the adoption of the sitting-up posture. The following theories have been put forward, from time to time in order to explain this important relationship —

1 *Field and Bock's Theory*³⁸ of "diminished venous return and cardiac output" Using the "carbon dioxide method" of determining the cardiac output, these workers³⁸ found the values in the standing, sitting and reclining positions to be in the proportion of 2 to 3 to 4. The reclining value was twice that observed in the standing position. This work was confirmed by Henderson and Haggard,⁶⁵ using the Ethyl Iodide method.

An increase in venous return to the heart during recumbency, has been proved indirectly by Moretz⁴⁰ and by Dutton,²⁸ who demonstrated an increase in the size of the heart in the lying-down position.

If this theory be proved correct, then the increased venous return to the heart in the recumbent posture would necessarily entail an increase in pulmonary engorgement, which in turn would induce dyspnoea by increasing ventilation. Adoption of the sitting-up posture (the orthopnoeic posture) on the contrary, would, by diminishing the cardiac output and venous return, cause a "falling-off" in the state of pulmonary congestion and hence alleviation in the state of dyspnoea.

Of late, Grollman⁴⁹ and Marshall,⁴⁰ both using the Acetylene method, have questioned the validity of the above contention, since they could detect no difference in the value of the cardiac output in the recumbent and erect postures. More recent determinations of the cardiac output by Donal and others²⁸ and by Schneider and Crampton⁴⁰ are, however, in accordance with the theory of Field and Bock.³⁸

2 *Hill's Theory*^{40, 68}—According to the theory of Leonard Hill, propounded as early as 1895, the alleviation of respiratory distress in the erect posture is due to a displacement of blood downwards into the splanchnic regions and into the lower extremities thus lessening pulmonary congestion. In its favour, are the following clinical and experimental observations viz (1) The superficial veins of the legs display an increase in size, in the erect posture, (2) Patients of orthopnoea often get added relief from the simple expedient of hanging their feet down from the side of the bed. (3) The plethysmographic experiments of Atzler and Herbst⁴⁰ have shown an increase in volume of the foot in the sitting-up and standing positions. (4) The ingenious experiments of Mosso⁴⁰

3 *Wollheim's Theory*¹²⁵ of the "withdrawal of blood from the rapid circulation". According to Wollheim,¹²⁵ in orthopnoeic subjects, the mere adoption of the erect posture reduces the "circulating blood volume" by 400 to 1200 CC. According to him, a goodly part of blood is withdrawn from active circulation in the erect posture, thus reducing the degree of pulmonary congestion.

4 *Bohr and Rubow's Theory*⁴⁰—They believe that in the erect posture, the flow of blood through the lungs is facilitated, there being

less resistance to the flow. This they ascribe to an increase in "middle capacity" (i.e., the average distention of the lungs) in the erect posture.

The relation of Orthopnoea to "vital capacity" and to the "resting ventilation ratio"

A reduction in vital capacity in the recumbent position, has been demonstrated by Christie and Beams.¹⁰ They found a difference in vital capacity between the upright and recumbent positions to be about 5 per cent in normal subjects and about 25 per cent in orthopnoeic subjects. The corresponding figures obtained by Calhoun, Cullen, Harrison and others,¹⁰ were 5 to 8 per cent difference for normals and 8 to 8 per cent of cases of congestive cardiac failure. In the series of orthopnoeics reported by Ernstene and Blumgart,³³ the difference in vital capacity readings for the two postures, worked out at only 8 per cent.

According to Harrison,⁵¹ dyspnoea is proportional to the "ventilation ratio" which is a far better guide to dyspnoea than either the vital capacity or the "ventilation." In heart cases, even though change of posture may fail to induce any significant alteration in the vital capacity or ventilation, the "ventilation ratio" is almost always significantly altered, there being an increase in the recumbent and a fall in the upright posture. The value of the "resting ventilation ratio" is much higher in the recumbent than in the sitting up posture, as demonstrated by Calhoun and his associates.⁵¹

As shown by Harrison,⁵¹ dyspnoea is a *threshold phenomenon* not unlike glycosuria. If a given case be at or near the threshold of dyspnoea, change of posture by inducing even a slight alteration of the ventilation ratio, will initiate respiratory distress or orthopnoea.

The Theory of "diminished cerebral blood-flow"—According to this theory, supported by Krehl, Sahlh,¹⁰² Herschfelder, Mackenzie,^{80, 81} Ernstene and Blumgart³³ and others, there is a rise of cerebral venous pressure in the recumbent posture which, by leading to diminution in cerebral blood-flow, induces a state of "oxygen-lack" or "oxygen-want" in the respiratory centre and hence, respiratory distress.

In support of this theory, one may cite the following observations viz (1) The demonstration by Ernstene and Blumgart³³ of a state of parallelism between the height of the venous pressure and the degree of orthopnoea in cases of cardiac failure. (2) Ernstene and Blumgart's³³ observation that in orthopnoeic patients, their respiratory distress in recumbency can be alleviated, at times, by simple flexion of the head on the thorax. (3) Eppinger, Laszlo and Schuremeyer⁴⁰ found, with the aid of the Theroströmuhler, that mere lowering of the head results in a diminution in the rate of blood-flow within the Internal Jugular Vein.

The following clinical arguments have been levelled against the theory of "diminished cerebral blood-flow" viz, (1) orthopnoea is frequently encountered in cardiac patients with perfectly normal venous pressure and with no engorgement of neck-veins. (2) severe venous engorgement and high-venous pressure are frequently encountered in cardiac cases, who exhibit no orthopnoea whatsoever, especially in cases of pulmonary heart disease and chronic constrictive pericarditis. (3) The orthopnoea of massive pleural effusions, pneumothorax and ascitis is not customarily accompanied by a rise of venous pressure.

(4) In spite of a deficient cerebral blood-flow, as in cases of peripheral failure with diminished cardiac output there is no accompanying orthopnoea. (5) As shown by Ferris and McGuire³⁷ in cases of superior vena cava obstruction, there are very high venous pressure values in the upper part of the body and yet there is often no orthopnoea at all.

Numerous objections have also been levelled against this theory by Harrison and his associates,⁶¹ on the basis of ingenious experiments, both in man and animals viz (1) By tying a blood-pressure cuff around the neck and inflating it to a pressure of 15 or 20 mm Hg (which is much higher than attained in heart-failure), Harrison⁶¹ failed to produce any respiratory distress. (2) By estimating the gaseous contents of arterial blood and of blood drawn from the internal jugular vein, in cases of orthopnoea, Harrison⁶¹ could not demonstrate any substantial "oxygen-difference" between the lying-down and sitting-up positions. (3) on the basis of animal experiments, Harrison and other⁶¹ maintain that oxygen-lack of the respiratory centre induces a form of respiratory distress that is different from that observed in cardiac failure cases.

*The Theory of Haldane, Meakins and Priestley*⁶⁰—They attribute the dyspnoea of recumbency to deficient aeration of blood. According to these authors⁶⁰ "expansion of the lungs" becomes inefficient or uneven in the lying-down position. Normally, this is compensated for by an increase in "respiratory depth" but in cardiacs with poor vital capacity, such a compensatory mechanism cannot be achieved with the result that the uneven lung-expansion, results in deficient aeration of blood within the lungs, during recumbency.

In support of this hypothesis, are the values of "oxygen saturation of arterial blood" in the upright and recumbent postures, reported by Calhoun and associates⁶¹. They found that some patients do show high oxygen-values in the upright posture.

In any case, this attractive hypothesis probably holds good for the minority of cases of orthopnoea only. Its role appears subsidiary. The physiological mechanisms, concerned in the genesis and alleviation of orthopnoeic dyspnoea, have been diagrammatically worked out, in Table 5 2 and 3.

TABLE II
THE PHYSIOLOGICAL MECHANISM OF ORTHOPNOEA

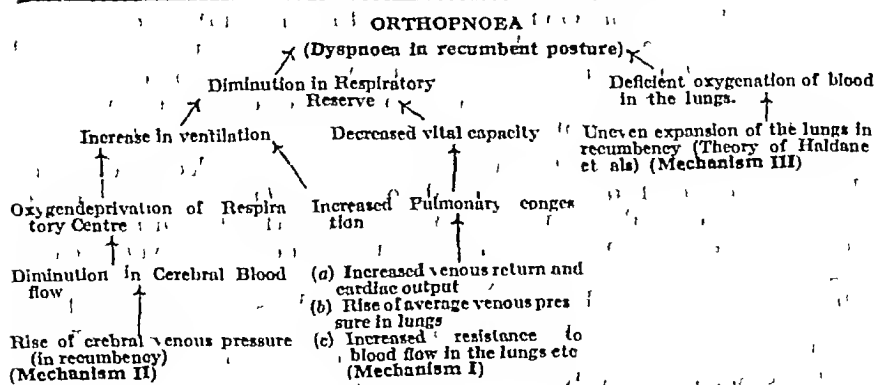


TABLE III

ILLUSTRATING THE MECHANISM OF "RELIEF OF DYSPNOEA" OR ORTHOPNOEA IN THE "SITTING-UP" OR "UPRIGHT" POSTURE

| RELIEF FROM DYSPNOEA OR ORTHOPNOEA (Sitting up or upright) | | |
|---|--|---|
| Improved cerebral blood flow ↑ Fall of cerebral venous pressure (Mechanism II) | Diminished pulmonary congestion ↑ (a) Diminished venous return & cardiac output (b) Cardiac displacement of blood tissue (c) Withdrawal of blood from 'rapid' circulation (Maldane et al) (d) Fall in the average venous pressure (e) Diminished resistance to flow of blood in the lungs (Mechanism I) | Better aeration of blood in lungs ↑ Even or uniform expansion of lung tissue (Mechanism III) |

TREPONNOEA

This interesting condition, recently studied and named by Wood and Wolferth,^{126,127} indicates a form of dyspnoea or respiratory distress that is present in one recumbent posture but is absent in others. Its main characteristics, as defined by Wood and Wolferth,^{126,127} are (1) That the distress occurs in one or other position only i.e. either lying on the left or the right side (2) Immediate relief is obtained by assuming a more favourable position (3) Distress does not appear immediately after the assumption of the unfavourable position, there being a latent period of from 10 seconds to 2 minutes (4) Although observed in many cases of congestive cardiac failure, the distress tends to be absent when systemic congestion is much more marked than pulmonary congestion

PATHOGENESIS

The following two theories of causation are in vogue at the present time viz

(1) *Wood and Wolferth's Theory*^{126,127}—They attribute the condition to a well-marked shift in the position of the heart, within the thorax, with resultant torsion of or pressure on mediastinal structures. The following evidence has been adduced in favour of this theory viz (a) That a "shift" can and does occur in the position of the heart, with changes in the position of the patient, is now generally accepted

(b) Wood and Wolferth found no constant alterations in vital capacity or in the "depth of breathing by alterations in the recumbent position of the patient (c) Wood and Wolferth^{126,127} could induce cardiac embarrassment in dogs by placing the animals in certain recumbent positions, after having severed previously the attachment of the heart to the diaphragm

(2) *Harrison's Theory*⁵¹—According to Harrison, trepopnoea is due to an increase in the degree of pulmonary congestion, in the unfavourable position. In his opinion, trepopnoea when noted in the left recumbent position is secondary to pulmonary congestion from one or more of the following possible mechanisms viz (A) a more rapid emptying of blood from an engorged liver into the heart, (B) obstruction of the venous return from the lungs secondary to mediastinal shift. Trepopnoea in the right recumbent position has been explained on the basis of

Dock's²⁷ observation, who found the average pulmonary venous pressure to be high in this position

In support of this theory of trepopnoea, Harrison refers to the somewhat similar postural relationship of cases of orthopnoea and also to the phenomenon of the latent period (already referred to)

PAROXYSMAL CARDIAC DYSPNOEA

This type of dyspnoea is frequently referred to as Paroxysmal Nocturnal Dyspnoea or as Cardiac Asthma

Innumerable theories have been propounded from time to time with a view to explain the causation of this interesting form of cardiac dyspnoea. In view of the fact that the great majority of these theories have been already abandoned, we have purposefully refrained in the paper, from any further discussion of the merits or de-merits of these obsolete theories. For the sake of completeness, however, we have given a short summary of these theories in Table 4

TABLE IV
THE CLASSICAL THEORIES OF CARDIAC ASTHMA (IN CHRONOLOGICAL ORDER)
(MANY ABANDONED)

| No | Date | Originators of theory | Theory |
|----|------|-----------------------------|--|
| 1 | 1882 | Hoppe | Excess of blood in the lungs compressing the air vessel and preventing the free admission of air |
| 2 | 1877 | Traube | Due to pulmonary congestion resulting in a Lungenanschwellung or encroachment of alveolar spaces by distended capillaries (preventing, effective ventilation of bloods), |
| 3 | 1878 | W. H. Welch | Inadequate emptying of Left Ventricle due to dilation as a result, the two ventricles pump unequal amount of blood, resulting in pulmonary oedema |
| 4 | 1891 | Von Basch | The Theory of 'Lungenstarre' Increased 'rigidity of lung tissue' resulting in deficient aeration of blood, |
| 5 | 1910 | Forges | Inadequate oxygenation of blood leading to 'acidosis' and stimulation of respiration |
| 6 | 1912 | Siebeck | Rigidity of lung tissues which by causing 'uneven aeration', leads to increased CO ₂ pressure in the arterial blood and respiratory stimulation |
| 7 | 1918 | Straub and Meier | 'due to carbon dioxide acidosis' |
| 8 | 1924 | Eppinger Von Papp & Schwarz | Due to (1) increased venous return to heart secondary to circulation acceleration and vaso dilation, and (2) a diminution in the functional capacity of the left ventricle secondary to vagus overaction |
| 9 | 1926 | Hess | "Due to the reflex effect of a myelomalacic heart on the pulmonary arteries" |
| 10 | 1927 | Wassermann | 'Reflex stimulation of the central Nervous System from the root of the aorta' |
| 11 | 1927 | Fraser | Diminished flow of blood through the Respiratory center |
| 12 | 1928 | Danzer | Due to increase of c.s.f. pressure during sleep |
| 13 | 1928 | Braunn | Passage (nocturnal) of fluid from tissues into the blood the plethora causing pulmonary engorgement and dyspnoea |
| 14 | 1931 | Gollwitzer Meier | Nocturnal passage of fluid from tissues into blood, the plethora causing pulmonary congestion which by leading to reduction in residual air, causes reflex stimulation of respiration |
| 15 | 1931 | Volhard | 'Cerebral Asthma', Same attacks of cardiac asthma secondary to ischaemia of the respiratory center |

PATHOGENESIS

As in the case of Exertional Cardiac Dyspnoea, we consider it advisable to study the pathogenesis of Paroxysmal Cardiac Dyspnoea from the points of view of (1) Predisposing factors and (2) Precipitating or exciting factors (the so called "trigger mechanisms")

Predisposing Factors —In the very great majority of such cases the predisposing factor has now been shown to be the factor of *pulmonary congestion* or engorgement. It is the factor that brings the patient near to the threshold of dyspnoea by lowering his "respiratory reserve"

The relation of pulmonary congestion to cardiac asthma, although established on a firm footing only of late, is by no means a newly discovered fact. It was recognised as early as 1882 by Hope⁷¹ in his first English treatise on Diseases of the heart. His contention was later supported by Traube¹¹⁶ in 1877 and by Welch¹²³ in 1878

Clinical evidence is definitely in favour of this theory of pulmonary congestion, (1) Cardiac asthma is more or less confined to cases of left ventricular failure or strain e.g., cases of hypertension, arteriosclerosis, aortic incompetence, etc., cases where pulmonary congestion is more or less a recognised feature. On the other hand, cardiac asthma is most unusual in cases of right ventricular failure or strain, where the congestion of blood-vessels is systemic rather than pulmonary (2) When right ventricular failure becomes super added on top of a left ventricular one, the pulmonary congestion is relieved whilst attacks of cardiac asthma become infrequent or may even disappear⁴⁰ (3) Clinical evidences of pulmonary congestion (viz., accentuated second sound in the pulmonary area, moist sounds in the middle-zones and lung-bases, fluoroscopic evidence, etc.) are demonstrable in all cases of cardiac asthma (4) Acute pulmonary oedema, a phenomenon shown by Welch¹²³ to be dependant on a state of pulmonary circuit engorgement, is very common in cases of cardiac asthma (5) Weiss and Robb¹²² have demonstrated definite evidences of passive engorgement of the lung-vessels in patients of cardiac asthma viz., a definite and consistent slowing of the pulmonary blood-flow during bouts of cardiac asthma, an increase in the blood-content of the lungs, a "hypertension" of the "lesser circulation" and a diminution in vital capacity

Cause of Pulmonary Congestion —When the left ventricle is weak or failing, the contractile power of its muscle becomes impaired. If the right ventricle, at the same time, continues to function normally, an engorgement of the pulmonary circuit is the only possible and logical issue. Such is then the most likely explanation of the pulmonary congestion in cases of cardiac asthma

*Harrison's observations*⁵¹ —In this connection, observations of Harrison and his associates on the respiratory functions of cardiac asthmatics is of great interest. They showed that during the interval between seizures, the ventilation shows a further rise whilst the vital capacity falls still lower. The "resting ventilation ratio" is raised by 25 per cent during "mild" and by even 100 per cent in severe seizures

The patient of cardiac asthma, prior to the actual seizures is, therefore, already "close to the dyspnoea threshold", any precipitating factor or cause, that tends to stimulate ventilation or reduce the vital capacity, will "set off" the paroxysm of cardiac asthma in such an individual, already predisposed or rendered "susceptible"

Precipitating or Exciting Factors—(the so-called "Trigger mechanisms") Many different factors have been incriminated from time to time, as the actual "trigger mechanisms" involved in the initiation or "firing off" of the cardiac asthma seizure, (for convenience, these factors have been enumerated in Table 5, with their essential characteristics).

TABLE V
THE PRECIPITATING FACTORS OR "TRIGGER-MECHANISMS" OF CARDIAC ASTHMA (CLASSIFIED AND EXPLAINED)

| No. | Precipitating Factor | Physiological Mechanisms concerned |
|-----|-----------------------------------|---|
| 1 | The "State of Sleep" | (1) Diminished, or depressed sensitivity of irritability of the nervous system during sleep (2) A displacement of blood from the infradiaphragmatic vessels into the pulmonary vascular channels, resulting in intensification of pulmonary congestion (3) Volhard's Theory: Respiration of edema fluid into the blood stream during the night hours (4) Diminution in coronary blood flow secondary to fall of aortic blood pressure in the night (5) Theory of Eppinger et al. Due to (A) Hypercirculation or circulatory acceleration and (B) a general increase in para sympathetic or vagal tone in relation to sympathetic tone (6) Due to an "active constriction" of the coronary arteries |
| 2 | Cough | (1) Reflex stimulation of respiration from rise or venous pressure within the main veins and right auricle (the "venous reflex" of Harrison) (2) Reflex respiratory stimulation from the "muscular effort" of coughing, through the intermediation of local nervous reflexes (Harrison) (3) By increasing the work of the heart. (4) Chemical alterations in blood due to defective exchange of gases in the lungs |
| 3 | Dreams and nightmares | (1) Rise of arterial blood pressure during dreams (Mac William) (2) Increased ventilation secondary to the state of apprehension or fear during nightmares. |
| 4 | Abdominal Distension | Reflex stimulation of respiration from distension of stomach, intestine, rectum or urinary bladder |
| 5 | Hunger | Due to either (1) a state of hypoglycaemia or (2) Hunger contractions of the stomach (Harrison) |
| 6 | Fatigue or overwork | Due to (1) Increased pH of blood from muscle activity or (2) Increase of pulmonary congestion secondary to increased cardiac output (with weakened left ventricle) |
| 7 | Increased Atmospheric temperature | Stimulation Respiration (Harrison) |
| 8 | Due to periodic Breathing | The phase of "dyspnoea" during periodic respiration may inaugurate a paroxysm of cardiac asthma. (Traube, Mackenzie) |

The following "factors" have been particularly stressed or discussed in the literature on cardiac asthma

I. *The state of sleep*—There is no doubt that the great majority of cases of cardiac asthma are "nocturnal" and wake up the patient from deep slumber. It is only natural, therefore, that attempts have been made in the past to discover some sort of mysterious relationship between the state of sleep and the actual paroxysm of nocturnal dyspnoea. The following theories have been propounded to explain this relationship

1. The theory of *decreased sensitivity or diminished irritability of the nervous system* during sleep normally even mild degrees of pul-

monary congestion are capable of reflexly stimulating the respiratory centre and inducing increased ventilation. In the sleeping hours, however, there is a diminished irritability of the central nervous system, with the result that much more severe grades of pulmonary congestion are necessary to reflexly stimulate the respiratory centre. The net result is that by the time the patient wakes up, the lungs are already too severely engorged. This theory awaits confirmation.

2 *Vollhard's Theory of Fluid resorption*^{110, 40}—This theory attributes the attack to a "resorption of oedema fluid into the blood-stream" during sleeping hours.

According to Vollhard,^{110, 40} even in cardiac patients with no apparent oedema, there is usually a considerable retention of water in the tissues (a so called "latent oedema"). During sleep, there is a supposed resorption of this oedema fluid into the blood-stream, with secondary hydraemia and augmentation of the work of the heart. If the left ventricle is weak or failing, the right ventricle deals more efficiently with this increased "load" and as a result, pulmonary congestion ensues. In support of Vollhard's hypothesis, the following observations may be marshalled, viz, (A) The clinical amelioration observed after the use of mercurial diuretics in cases of cardiac asthma (B) Ingestion of large amounts of fluid or water by mouth, tends to precipitate further attacks of cardiac asthma, (C) good results have been reported, in these cases of Vollhard, with the use of "dry diets."

Against Vollhard's theory is the clinical observation that even in cardiacs completely at rest in bed during the daytime (who are both recumbent and asleep during the daytime), nocturnal attacks of cardiac asthma are frequent.

3 *The Theory of Hypercirculation of Eppinger, Von Papp and Schwarz*³²—According to this conception, there are two factors responsible for cardiac asthma, viz, (A) a *hypercirculation or circulatory acceleration*. This is particularly so in the evening hours, the rapid flow of blood from arteries to veins being due to a combination of factors, like increased production of lactic acid, nocturnal retention of carbon dioxide, etc. The rapid flow of blood leads to an increase in "venous return", which in turn embarrasses the left ventricle. (B) A general increase in *parasympathetic or vagal tone* as compared with sympathetic tone, a condition associated with sleeping state and which, according to Eppinger and others, leads to a decrease in tone of the left ventricle.

Recent observations are against this unusual theory.

4 *The theory of the "recumbent posture"*—According to this theory, paroxysmal nocturnal dyspnoea is somewhat allied to orthopnoea, the attack being attributed to a "passive slipping down" of the patient in bed i.e., to the adoption of a recumbent posture. The latter accident leads to "displacement of blood from the infradiaphragmatic vessels to the pulmonary circuit" with corresponding intensification of pulmonary congestion.

5 *The Theory of reduced coronary blood-flow*—During sleep, in normal individuals, there is a small drop of aortic blood-pressure, as proved by Grollman. In cases of hypertension or heart disease, on the other hand, the corresponding drop of pressure during sleep may be

considerable even amounting to 40 mm Hg drop in the systolic pressure (Harrison)⁵¹. It is possible that a big drop of this order may, by reducing the coronary circulation, lead to ischaemia and further weakening of the left ventricle

6' *The Theory of "active coronary constriction"*—It has been claimed by some workers (Cf Harrison)⁵¹ that the state of sleep induces a state of "active constriction" of the coronary arteries which in turn may lead to further cardiac embarrassment. Evidence in support of this contention is wanting

II *Unpleasant dreams and nightmares*—Their importance is suggested by the frequent observation of the cardiac asthmatic who claims to have been awakened by a "bad dream". The modus operandi of this factor is doubtful, several views have been put forward—

(1) The apprehension or fear associated with a nightmare may induce an increase in ventilation, in a cardiac patient with congested lungs, who is already at the threshold of dyspnoea, even a mild increase of ventilation will cause respiratory distress. This has been demonstrated by Harrison⁵¹ who noted the effects on ventilation of various stimuli e.g., smashing of burned out electric light globes, dropping tin plates on the floor, etc. They demonstrated a marked increase of ventilation after these procedures

(2) *Due to rise of arterial blood pressure*—Mac William⁴⁰ has demonstrated well-marked rises of both systolic and diastolic pressures during dreams. The increment in systolic pressure may amount to 50, 60, or 70, mm Hg. or even more. Such rise can easily induce pulmonary engorgement, in a case with a functionally poor left ventricle.

III *Cough*—According to Harrison,⁵¹ this is one of the most common of the precipitating factors of cardiac asthma. He has adduced considerable evidence to show that in patients at least of cardiac failure, coughing plays a dominant role in "initiating" paroxysms of cardiac asthma while in patients who are dyspnoeic to begin with coughing increases their distress. Harrison⁵¹ showed by experiments that (1) in ambulatory patients with exertional dyspnoea, the act of coughing induces shortness of breath and (2) that in decompensated patients with continuous dyspnoea, the latter increases enormously after coughing and may even go into cardiac asthma or pulmonary oedema.

How does cough operate in precipitating attacks of cardiac asthma?

(1) *Reflex respiratory stimulation by causing a rise in venous pressure* Harrison⁵¹ has demonstrated the "venous reflex" that any increase in press. in the right auricle or in the central terminations of the venae cavae results in a reflex acceleration of breathing. During coughing there is sudden rise in intrathoracic pressure, during the inspiration immediately after coughing, blood is suddenly sucked into the main veins and right auricle with resultant stimulation of breathing. (2) *Reflex respiratory stimulation from the "muscular effort" of coughing* according to Harrison⁵¹ cough is a violent muscular effort which like other muscular movements causes respiratory stimulation through the intermediation of local nervous reflexes (see elsewhere). (3) *Cough as a form of muscular effort*, tends to increase the work of the heart and tends to embarrass its working. (4) It is possible that cough may interfere with the exchange of gases within the lungs and thus introduce chemical alterations in the blood with resultant stimulation of the respiratory centre.

The vicious cycle of cough—It has been shown by Harrison⁵¹ that once cough arises, a vicious cycle is established which tends to perpetuate the state of dyspnoea. Cough initiates deep breathing which in turn tends to cause cough, the cough again sets the cycle going. This phenomenon is repeated over and over again.

Why "cough" is more likely to precipitate cardiac asthma in the night time rather than in the day time?—Harrison⁵¹ has the following explanation to offer. During sleep, the "reflex irritability" or sensitiveness of the C N S is depressed and hence a stronger stimulus is required to initiate the "cough reflex" than is necessary during the working hours. The cough reflex is, therefore, poor, expectoration collects in large amounts within the bronchial tree. When the accumulation reaches a certain level severe coughing suddenly starts and initiates hyperventilation. The patient whose vital capacity is already poor and who is already at the threshold of dyspnoea, becomes dyspnoeic not only is there an unduly strong stimulus but there is also a sudden increase in irritability of the respiratory centre attendant on the sudden change from a sleeping to a working state.

IV Due to the "dyspnoeic phase" of "periodic breathing"—In some cardiacs the respiration tends to become "periodic" when they fall asleep. Both Traube¹¹⁰ and Mackenzie^{80, 81} have suggested that the increased breathing phase or the dyspnoeic phase during such periodic breathing may be instrumental in inaugurating paroxysmal dyspnoea.

V Increase in atmospheric temperature—The importance of this factor in some cases has been stressed by Harrison⁵¹ on the following grounds—(1) Patients often volunteer the information that attacks of cardiac asthma become more frequent or severe during hot weather or in the presence of too many bedclothes. (2) Harrison⁵¹ placed some patients in a "warming cabinet" with the head outside. He found that on raising the temperature within the cabinet to 55°C, the ventilation showed a well marked increase in some cases. This factor probably operates by stimulating respiration.

VI Distension of abdominal viscera e.g., stomach, intestine, rectum or urinary bladder. In support of this contention are the following facts—

- (1) Many patients complain of excessive flatulence or distension prior to the attack of C asthma.
- (2) Many patients notice attacks after a heavy evening meal or when they are constipated or when the urinary bladder is full.
- (3) Relief frequently experienced after passage of flatus or urine or faeces or by avoiding the evening meal.
- (4) Artificial distension of the colon with 100 cc Barium paste and of the bladder by 50 cc saline solution in animals by Harrison gave rise to "accelerated breathing" in some animals. *Modus operandi*. Stimulation of ventilation.

VII Hunger.—According to Harrison,⁵¹ this factor may operate in some cases because patients in rare cases volunteer the information that hunger initiates the attack whilst Harrison has observed relief after

the congestion of food or drink. *Modus operandi* of this factor not known though Harrison⁵¹ suggests 2 possibilities

(1) A state of hypoglycaemia may be responsible or

(2) Hunger contractions of the stomach

VIII A state of fatigue—"Overwork on the preceding day" It is a common observation on the part of the patient that Cardiac asthma attacks are most frequent after a day of undue activity or exertion. This is explainable on the following grounds

(1) An increase in the degree of pulm Congestion from increased metabolic demands. During exertion, the blood supply increases the venous return &c. output increase. If the left ventricle is weak, then the right ventricle will induce pulm Congestion

(2) There may be a slight increase in p-H of blood from acidity

Course of Cardiac Asthma—There are 3 courses open to an attack⁵¹

I A spontaneous termination—The attack passes off spontaneously after a variable duration of a few records to several hours. According to Pratt,⁵² the average duration is 1 hour

The attack is brought to a stop thus —

1 By the assumption of a sitting up or erect posture, the pulmonary congestion is relieved as blood flows downwards

2 Removal of the causative factor e.g., expectoration of mucus, passage of flatus or defaecation, a drink if hungry, etc

3 The dyspnoea may wash out cough CO₂ to lead to respiration depression and arrest of the seizure

II Response to sedatives e.g., morphia *Modus operandi*—The morphia benefit is due to a depressant effect on the respiratory centre; thus lowers its sensitivity to reflex stimulation. In almost all cases, where relief follows morphia there is a marked diminution in ventilation and often a fair rise in vital capacity (Harrison)⁵¹

III Development into pulmonary oedema which recovers or proves fatal. Pulmonary oedema is simply a severe form of severe form of cardiac asthma where the pulmonary engorgement has become severe enough to "allow a rise of the pulmonary intracapillary pressure above a certain critical level" (Harrison)⁵¹ probably "above the counteracting osmotic pressure of the plasma proteins" (To be continued)

Critical Notes and Abstracts

THE PSYCHOSOMATIC CONCEPT

In discussing the psychosomatic concept Felix Deutsch suggests that general medical men can learn to treat psychosomatic disorders by learning firstly to make a psychosomatic diagnosis, which means the demonstration of the proof of the inter-relationship of body and emotional symptoms and their classification. It is suggested that general physicians should treat patients until the symptoms for which the patient came disappear.

The symptom disappears either when the need for the bodily expression is removed, or when the bodily symptoms are reconverted into emotional symptoms. Treatment should be discontinued when no more body symptoms exist. When the patient who had suffered previously from organic symptoms suffers now from emotional symptoms, he will accept more easily treatment by a psychiatrist. Patients should preferably not be transferred to the psychiatrist until they have had a preliminary treatment by the physician. It is suggested that an internist can specialize in the field of psychosomatic medicine by becoming theoretically and practically acquainted with the psychology of the normal personality, child psychology, psychology of adolescents and adults, of involution, of old age, and with the theory of adjustment.

Psychotherapy of the neuroses and psychoses and emotional problems of the sick should be studied in great detail, including the indications and limitations, of psychotherapy. It also is advantageous that the specialist in psychosomatic medicine have his own analysis. The psychosomatic background of several conditions is discussed, including that of ulcer and colitis.

The author concludes that a knowledge of personalities of patients with psychosomatic disorders can prevent wrong approach to the patient and can protect the physician against showing inadequate response to the behaviour of the patient. In understanding the personality pattern he will not take this behaviour pattern at face value since it has unconscious motivation and is a symptom of the disease.

(Deutsch, Felix: Boston, Mass. "The Psychosomatic Concept" *Acta Medica Orientalia* 7:22 42 March 1955)

AUREOMYCIN A NEW ANTIBIOTIC WITH VIRUCIDAL PROPERTIES

Louis T. Wright et al. report on successful treatment of 25 cases of lymphogranuloma venereum with aureomycin, a new antibiotic supposedly having virucidal properties. The substance aureomycin was obtained from streptomycin which gave a promise of possessing unusual antibiotic properties. Because of a striking spectrum of activity exhibited by this antibiotic against many rickettsiae and certain viruses, the authors studied its action in 25 selected cases of lymphogranuloma venereum. The cases were divided into three groups, those with (1) buboes, (2) lymphogranulomatous proctitis, with or without ulceration, and (3) benign cicatricial rectal strictures.

The drug was administered by intramuscular injection in daily dosage varying from 10 mg. to as high as 40 mg. In the eight patients

with buboes, a decided reduction of size of the nodes occurred at the end of four days' treatment. Three patients with proctitis showed decided improvement in two instances after four days of treatment and in another instance after eight days.

Proctoscopic examination at the end of treatment showed normal rectal mucosa. Fourteen patients with benign rectal stricture due to lymphogranuloma venereum were studied and showed no gross pathologic change in the fibrous rectal stricture, although there was decided decrease in rectal pain, discharge and bleeding. There was also an increase in the diameter of the stool. On the basis of past experience the authors believe that the 25 cases of lymphogranuloma included multiple strains of the virus and that therefore the effectivity of aureomycin is not limited to a single strain. The clinical results obtained in this series of cases warrant further extensive research and clinical trial of this antibiotic.

(Wright, Louis T., Sanders, Murray; Logan, Myra A.; Tricot, Aaron, and Hill, Lyndon M., Aureomycin: A New Antibiotic With Virucidal Properties", J. A. M. A. 138-408-412 October, 1948)

OBSTACLES ENCOUNTERED IN RECOMMENDING PSYCHOTHERAPY

Discussing the obstacles encountered in recommending psychotherapy, Bernard C. Meyer refers to a recommendation in 400 consecutive cases that the patients receive psychotherapy after having been seen at the consultation service in the Mount Sinai Hospital in New York. In a six-month follow-up by letter, replies were received from 270 individuals. One hundred thirty did not reply. In 41 instances the referring physician had lost contact with the patient and was unable to provide any information.

Of the remainder, 19, or seven per cent, had procured some type of systematic psychiatric therapy. One patient undertook psychoanalysis, six others received some undescribed form of long-term psychotherapy, one patient attended a mental hygiene clinic, two received shock therapy and three were hospitalized in mental institutions. Six others were seen by psychiatrists for a total of less than five visits each. Actually, only 13, or less than five per cent of the 270 secured anything approaching adequate psychotherapy.

Including the 130 patients from whom replies were not received, the percentage of the total number of receiving psychotherapy was 31 per cent. However, 74, or 36 per cent, of the 210 patients who failed to receive psychotherapy were said to have improved for one reason or another. The author concludes that the failure to undertake recommended psychotherapy is based on three considerations: (1) the resistance of the patient to the idea of undertaking psychiatric therapy, (2) the lack of cooperation or understanding on the part of the medical practitioner, and (3) the lack of psychiatric facilities to meet the needs and financial capacities of the patient.

The attitude of the public toward psychiatry and psychiatric illness is being influenced through educational and other channels so that some degree of insight for a small segment of the population has served to ameliorate the stigma of neurosis. However, in general, the public still does not differentiate too well between the neurosis and psychosis and the author considers that greater enlightenment concerning the aims and

goals of modern psychiatry will aid much in lessening the barrier which so many individuals erect against recognizing emotional determinants of their suffering

(Meyer, Bernard C. New York, N. Y. 'Obstacles Encountered in Recommending Psychotherapy' *Journal of Mount Sinai Hospital* 15:90-93 July-August, 1948)

STREPTOMYCIN IN THE TREATMENT OF TUBERCULOUS SINUSES

Benjamin L. Brock reports on treatment with streptomycin of a series of 12 patients with a total of 60 draining cutaneous tubercular sinuses. The average duration of draining sinuses prior to institution of treatment was 24 months. Eleven of the patients were Negroes and one was white. In all but two of the patients draining sinuses originated in bone. Tubercular etiology was proved in all cases either by biopsy or culture of sinus material. Only one of the patients had active pulmonary tuberculosis. A dose of 1.8 grams of streptomycin per day for 90 days was given to six of the patients and for 150 days to the remaining six patients.

Toxic reactions were observed but were not sufficient to justify discontinuance of treatment. Clinical signs of improvement were manifested soon after treatment was begun in 11 of the 12 patients. Emaciated patients gained weight rapidly, the average gain in weight being 15 pounds. Nine of the 60 sinuses closed within one to four weeks, nine within six to eight weeks, 30 within the 10th or 12th week and 11 within 13 to 20 weeks of the start of chemotherapy.

Induration and associated tenderness around the sinus tracts disappeared as early as one month after treatment was begun. Of the total 60 draining sinuses only one continues to drain eight months after initiation of treatment and this one shows definite improvement. The average time which has elapsed since treatment without recurrence is four months.

(Brock, Benjamin L., Clinical Director, Veterans Installation Oteen, N. C.: 'Streptomycin Treatment of Tuberculous Sinuses' *The American Review of Tuberculosis* 58:35-37 July, 1948)

PATHOGENESIS OF HUMAN BRUCELLOSIS WITH RESPECT TO PREVENTION AND TREATMENT

From a complete study and report on the pathogenesis of human brucellosis, Wesley W. Spink concludes that brucellosis is a major problem in public health in some sections of the United States with indications that the incidence of the disease is on the increase. Reservoirs of the disease are especially cattle, swine and goats, the disease being transmitted directly or indirectly to humans from animals and rarely, if at all, from human to human. Intracellular parasitism results from the invasion of tissues by *Brucella* resulting in the characteristic proliferation of epithelioid cells and giant cells. Complications include destructive osseous lesions, subacute bacterial endocarditis, encephalitis,

and grossly suppurative lesions Hypersensitivity of tissues to antigens of *Brucella* is a constant feature of brucellosis

The most satisfactory treatment to date for both acute and chronic cases of brucellosis is a combination of streptomycin and sulfadiazine From a study of 17 patients with a maximum follow-up period of one year the author concluded that the clinical course of both chronic and acute brucellosis is shortened by this combined therapy The combined therapy is effective against complications of brucellosis, such as sub-acute bacterial endocarditis and spondylitis Recommended dosage is 0.5 gram streptomycin intramuscularly every six hours for two weeks and three to four grams of sulfadiazine administered orally at the start of streptomycin therapy and then one gram every four hours for a total of two weeks Thus far, no streptomycin-resistant strains of *Brucella* have been recovered from patients as a result of this combined therapy

The author considers that the ultimate elimination of human brucellosis depends upon eradicating the disease from domestic animals Other preventive measures, such as compulsory pasteurization of all milk destined for human consumption and the pasteurization of all milk utilized for butter and cheese production, are indicated

(Spink, Wesley W., University of Minnesota, Minneapolis, Minn.: "Pathogenesis of Human Brucellosis with Respect to Prevention and Treatment" *Annals of Internal Medicine* 29: 238-258 August, 1948)

MANAGEMENT OF THE NEPHROTIC SYNDROME.—

(GEORGE E. FARRAR, JR., M.D., CHARLES F. SACKETT, M.D. and JOAN H. LONG, M.D., *The American Practitioner*, November, 2-194-197)

The nephrotic syndrome presents a difficult and trying therapeutic problem Specific treatment is not possible until the etiology is more thoroughly understood In general, the nephrotic syndrome is the clinical manifestation of protein deficiency with hypoproteinemia, edema (without evidence of congestive heart failure), impaired absorption and utilization of protein as shown by albuminuria

Treatment has followed several lines An attempt to increase the colloid osmotic pressure of the blood by the intravenous administration of amino acids, human albumin, plasma, globin, or acacia, as well as by increasing the protein in the diet, and attempt to bring about diuresis by using an acid or neutral ash, low-sodium diet, and the administration of diuretics, and an eradication of foci of infection by drainage and the use of suitable chemotherapeutic or antibiotic agents

Diet—An acid-ash, high-protein, low-sodium diet is a simple and satisfactory diet to use for the nephrotic syndrome Initially there should be six small feedings daily, each feeding consisting of one cup of milk and one egg or two slices of bread or one cup of cereal with butter, sugar, spices, and flavouring as desired This supplies about 60 Gm of protein daily A low-sodium milk powder is available (Lonalac-Mead-Johnson) When the patient is able to eat a full diet, the next and final diet should consist of three eggs, a quarter or a half pound of meat fish, or fowl, and six slices of bread or servings of cereal These meals should also provide not more than two cups of milk, one cup of vegetables, and one cup of fruits The following may be eaten as desired, sugar, butter, gelatin (Jell-O), prunes, plums, and cranberries Coffee

and tea may be taken if not otherwise contraindicated. This diet provides 90 to 130 Gm of protein daily. Food and foodstuffs to be avoided are salt, soda, salted butter or bread or meat, cheese (except cottage), lima beans, spinach, dates, and raisins.

Fluids—Daily 1,500 cc or more should be taken by mouth along with the acid-ash diet.

Amino Acids—Since it is desirable that the daily protein consumption be 2 or even 3 Gm of protein per kilogram (2 1/2 lb) of body weight, it is often necessary to augment the dietary protein intake by means of amino acids. This may be accomplished by 50 to 100 Gm of a protein hydrolysate (equivalent to 75% protein) orally or intravenously daily. For intravenous injection a 5% solution in 5% dextrose in distilled water is given at a rate of 5 to 20 Gm of amino acids per hour. In nephrotic crises amino acids intravenously daily are important in addition to penicillin and/or sulfadiazine.

Protein Diuretics—*Salt-poor Normal Human Serum Albumin*. This is a salt-poor substance that has the same viscosity as whole blood but is osmotically more active. Five grams in 20 cc of diluent contain only about 0.15 Gm of sodium chloride and these 20 cc are equivalent to approximately of 100 cc of plasma. The dose is 25 Gm (100 cc) twice daily intravenously given very slowly. A single daily dose of 50 Gm in 300 cc or more of 10% dextrose in distilled water intravenously may be given at a rate of 10 to 20 Gm per hour. Albumin must be given for three to four weeks. In active or incipient congestive heart failure this material must be used very cautiously. Although salt-poor normal human serum albumin parenterally provides the largest amount of protein, it has two important drawbacks,—it is not readily available and it is expensive. Unfortunately, a considerable portion is lost in the urine.

Normal Human Plasma—This protein material is less effective than the above because it provides less albumin and contains at least 5 Gm of sodium chloride per liter. The dose is 750 cc requiring 1,500 cc whole blood to 1,000 cc daily intravenously.

Globin, modified from human erythrocytes, is used in the same way as albumin and with similar results.

Other Diuretics—*Urea*. This may be given in 15 Gm doses two to four times daily in fruit juice for one to three weeks. It is contraindicated when azotemia is present and during its use weekly determinations of the blood urea nitrogen should be made.

Potassium Nitrate, Potassium Chloride, Ammonium Chloride, or Ammonium Nitrate—Any one of these drugs may be used in 3 Gm doses three times daily after meals as half-gram enteric coated tablets for three days or longer at a time. With potassium salts the patients should be watched for arrhythmia and with ammonium salts for acidosis.

Dried Thyroid—This is to be used in 0.06 Gm doses daily and may be increased by 0.06 Gm daily at weekly intervals until diuresis or toxic manifestations occur.

Acacia—After diet and diuretics have failed to relieve edema, 500 cc of 6% acacia and 0.06% sodium chloride in distilled water may be given intravenously slowly on alternate days for three (at the most,

six) doses and 2 cc of mercuraphylline injection (U S P) intravenously on alternate days

Gelatin or Pectin —These have been used in the same way as acacia

Other Measures —With the recent emphasis on the role of abnormal capillary permeability in the nephrotic syndrome, it has been suggested that rutin may be beneficial. Calcium salts parenterally decrease this abnormal permeability but nitrogen retention may develop

PSYCHOTHERAPY IN GENERAL PRACTICE —(LESLIE A OSBORNE, M D , Buffalo, New York in *New York State Journal of Medicine*, December, 47 2593-1596)

The medical profession has been reminded forcefully by World War II that it is not prepared adequately to meet its psychiatric responsibilities. All too often psychiatry has been remote from general medical thinking. Illness treated in psychiatric hospitals represent late stages of disturbances which originated in the home and the community. Until we learn to deal effectively with the early stages and their etiologic factors, we will see the casualty lists continue to mount.

To obtain early recognition and treatment, psychiatry must move from the hospital to the community, from the specialist to the general practitioner. He is in the community where these things happen, he is in confidential working relationship with patients and families, and he alone can be early enough on the scene to diagnose early difficulties. In most instances the specialist sees patients after the family physician has recognized the nature of the difficulty and referred them to him for treatment.

This makes it imperative that practicing physicians have an understanding of early diagnosis, factors producing psychiatric disorders, and the means whereby effective therapy and prevention can be accomplished.

In psychiatry the primary pathology lies in the relationship between persons, secondary effects on physical health are common. Sociology deals with interaction of these and the group considerations which impinge on individual lives.

For effective psychotherapy as for any treatment, the foundation must be accurate understanding of the condition being dealt with. The most potent diagnostic means physicians have in psychiatry—perhaps in medicine, too, is a well-known history. To obtain this we need to win the confidence of the patient, we need to listen and encourage spontaneous telling of the patient's story, and when questioning is needed, we need to know what to seek and how to interrogate. This takes time, but it is time well invested. If time is not spent in careful investigation so that early treatment can be instituted, it will be wasted in ineffective and unsatisfactory contacts later. Many neurotic patients give a history of treatment by one doctor after another. Sedatives, vitamins, endocrine products, physio-therapy, and reassurance have been given but a psychoneurosis is a condition in which physical or nervous symptoms are an indirect expression of some difficulty of personal adjustment.

There are three main parts to a psychiatric history. The first is the patient's account, as much as possible given spontaneously, of his difficulty. The second part consists of rebuilding the personal atmosphere in which early and later development of personality took place. The

influence of parents and home conditions is very strong. The family physician has the advantage of knowing some of the background already. We are often far too cursory in our inquiry into family history. A family history is not a recital of "Father-55-a & w, Mother-d 54 diabetes." It is the determination of the experiences the patient had in relation to those who helped—or sometimes did not help—his start in life, and his subsequent dealings with them. In a recent consultation where surgeons had recognised neurotic basis for complaints of a patient referred in for abdominal operation, the family history was listed as "negative." The patient's parents had separated before she was born, her mother refused to take care of her, she was placed in a foster home, and her foster-father committed suicide when she was nine.

The third part of a psychiatric history is personal. Knowing the general background and the people of most importance in it, a systematic account of the patient's life can be obtained. There are some things patients will tell readily, some they will tell after confidence has overcome reluctance to divulge intimate matters, and some which will come to the patient's consciousness during the process of treatment. If we do not listen, we will not hear any of these. If we are not trustworthy and tactful, we will not hear the second group. If we are not patient and understanding, we will not hear the third. Yet the deeper material is the most valuable, diagnostically and therapeutically.

What has just been said about the doctor's attitude determining the extent to which the patient reveals inner difficulties brings us to the point that psychotherapy has already begun when we start investigation. It is not therapy as we construe it pharmacologically or surgically, it is not done with needles or lights or massage. The physician himself by his own interest, maturity, and understanding is the therapeutic agent. What the patient needs and seeks is a wise friend and counselor, one who will respect confidences, not embarrass or laugh at him, one who will help him find a way out of a maze of difficulties and teach him how to avoid getting into such trouble again.

Psychotherapy of the psychoses and severe psychoneuroses is a matter for those with specialist training, as major surgery belongs to the surgeon. There is a great deal of what we might call minor psychotherapy which can best be done by the family doctor. When investigation has indicated that trouble is not too deeply seated, he can proceed with confidence to help the patient to help himself.

Weir Mitchell once said that the most important prescription a doctor ever gives is advice. Advice, however, is very potent medication, an unsound advice can have decidedly harmful effects. It should never be given lightly, and always the probable effects of the advice if taken should be fully worked out. The best form of advice is that in which the patient works out with the help of the doctor his own idea of what is wisest for him to do. Our function is that of a catalyst, not a reagent.

Psychoneuroses are substitutive reactions, the physical or nervous symptoms are "stand-ins" for some difficulty in adjustment. The patient comes with stomach-ache or insomnia or heart pounding or unreasonable anxiety about heart, logically he comes to his doctor and the latter investigates his physical condition. Differential diagnosis must be made between similar symptoms of dissimilar origin, as for

example, between vomiting as an expression of appendicitis, and an expression of disgust

Disproportion between complaint and organic findings may suggest neurosis, but diagnosis by exclusion alone is not enough. The patient does not want to know what is not wrong, he wants to know what is

Physical examination should not be curtailed because neurotic difficulties exist. One patient who was referred to the psychiatric clinic with digestive complaints had not been X-rayed because of the neurosis he had a duodenal ulcer

We often find neurotic patients in situational difficulty, but outer troubles of themselves do not produce neurosis. I am often in situational difficulties on the golf course, and if you put my ball back on the fairway for me I will soon be in trouble again. The expert can get out of trouble much better than I can, but he does not often get into the predicaments I do. So with our neurotic patients. Their difficulties are there, but something within themselves helped get them there, and if we simply remove them from their home or marriage or job we accomplish virtually nothing, we need to help them learn how to play the game of life better, to keep on its fairways, and, if they do get in its rough or its bunkers, to extricate themselves quickly

The medical profession cannot ignore the disastrous results of missed diagnosis and inappropriate treatment of psychiatric disorders. We need to recognize the chronic invalidism that the unresolved psychoneurosis represents, and to note the frequency with which operations, heavy sedation, irrelevant medication, and superficially conceived advice have complicated the difficulty while the basic process has continued unchecked. We must recognize the serious fallacy of the statement, "There's nothing wrong with you" or "It's all your imagination." Several years ago a depressed business man went to his doctor and was told after a physical examination there was nothing wrong with him, to go away and forget it. He went away and shot himself. When a patient is within half an hour of threatened death from hemorrhage or shock we do not take it lightly. We need to develop an equally sensitive diagnostic conscience for psychiatric disturbances as we have for organic

These are but a few aspects of a subject of great clinical and practical importance. The need for psychiatric service to the community is great and urgent, the small number of specialists we have is grossly unequal to the demand. We must train medical students during their course, we must develop psychiatric services in general hospitals where interchange of knowledge between internist and psychiatrist can take place readily, we must make postgraduate instruction available for those who recognize the need but have not had the basic training

Medicine has tackled some formidable problems before and come out the winner. As we reduce and finally prevent the tragedies that we call mental and nervous diseases, we will be equaling and perhaps exceeding any of the greatest victories man has yet achieved in his long struggle with the ills that beset his kind

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Original Contributions

CARDIAC DYSPNOEA

A PHYSIOLOGICAL APPROACH TO ITS PATHOGENESIS

(WITH A REVIEW OF THE MEDICAL LITERATURE)

by

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(Continued from last issue)

PERIODIC BREATHING OR CHEYNE-STOKES RESPIRATION

Although certain authors have continued to regard periodic breathing and cheyne-stokes respiration as one and the same condition, it is perhaps more accurate to regard the latter as one variety of the former. Periodic breathing, strictly speaking, may be of one of two types viz, (1) *Cheyne-Stokes respiration*, originally noted by Nicholas⁴⁰ in 1786 and later described in detail by Cheyne¹³ in 1818 and by Stokes¹³⁰ in 1854. (2) *Biot's breathing*⁶, as first described by Biot⁶ in 1876.

These two subdivisions of periodic breathing can be distinguished by attention to the following characteristics viz, (1) whilst Biot's breathing is more or less a monopoly of intracranial diseases, including meningitis, cheyne-stokes respiration is encountered with much greater frequency in a variety of disorders, including hypertensive heart-disease, narcotic poisoning, high altitudes and intracranial disorders. (2) Whilst in Cheyne-stokes respiration there is a gradual waxing and waning of the respirations with apnoeic pauses, in Biot's breathing, all the registered breaths are of the same depth or amplitude with no attempt at graduation.

Pathogenesis—The causation or pathogenesis of Cheyne-Stokes respiration has not, as yet, been satisfactory elucidated, especially in cardiovascular disorders. There is, however, sufficient evidence to suggest that one or more of the following factors or pathogenetic "mechanism" may be involved in the initiation of this form of respiratory disorder. It is possible that while in some cases only one of the following factors is operative, in others, three, four or even five of the factors may be jointly involved in the process of initiation.

Pathogenetic mechanisms or factors—(1) *Oxygen-lack or Oxygen-deficiency*—The importance of this factor has been emphasized by numerous authors.

In favour of the importance of this factor, we can cite the following evidence viz, (1) The clinical observation of Pembrey and Allen⁴⁷ that normal respiration may be restored in cases of Cheyne-Stokes

breathing by the inhalation of high concentrations of oxygen. Other authors have, however, reported such relief in only a small percentage of cases and as such, the relief is only partial or temporary, (2) The tendency for normal individuals to develop this form of respiratory disorder at high altitudes or in the course of "mountain sickness", (3) "voluntary hyperventilation", which induces anoxaemia, has been shown by Douglas and Haldane,²⁹ to be capable of initiating Cheyne-Stokes respiration. They made the further observation that if such hyperventilation be carried out in a "atmosphere rich in oxygen", the breathing which ensues is not periodic but regular. (4) King and Harrison⁵⁷ made a study of arterial blood samples of dogs, collected during the periodic breathing after overventilation. From the behaviour of oxygen and CO₂ gases, they were able to deduce the importance of oxygen-lack in periodic breathing, (5) Harrison⁵¹, using a spirometer filled with oxygen, tried to induce Cheyne-stokes respiration in dogs by overventilation. The experiment proved a failure until the oxygen in the spirometer was replaced by air.

That *anoxaemia is not essential* for the initiation of Cheyne-Stokes respiration is certain from the following evidence. (1) As convincingly demonstrated by Uhlenbruck¹¹⁷, Anthony, Coh, and Steele,¹ Harrison and others,⁵¹ the majority of cases of Cheyne-Stokes respiration remain unaffected or "periodic", even after the inhalation of high concentrations of oxygen. (2) Cases of Cheyne-Stokes breathing have been reported by Resnik and Lathrop,¹⁰⁰ where the oxygen saturation of arterial blood remained perfectly normal during phases of periodic breathing. In 7 of 18 patients studied by Harrison and Wilkins,⁴⁰ during bouts of periodic breathing, the oxygen-saturation of arterial blood remained over 90 per cent, in 4 cases it remained over 93 per cent.

That *severe anoxaemia* may exist at times in the complete absence of any periodic breathing is also certain. In cases of chronic extensive pulmonary disease and in congenital heart cases, there may be severe degrees of anoxaemia for months (with oxygen saturations below 50 or 60 per cent) and yet the breathing remains quite regular. It is possible that some other factor or factors are also necessary in conjunction with oxygen-lack.

2 *Carbon dioxide deficiency*—The importance of this factor in some cases of Cheyne-Stokes respiration has been proved by the following observations. (1) The hyperventilation experiments of Douglas and Haldane²⁹ and of Harrison⁵¹ confirm the importance of carbon-dioxide lack, overventilation, which washes out carbon-dioxide, initiates periodic breathing. (2) The clinical observation of Pembry and Allen⁹⁷ that inhalation of CO₂ in cases of Cheyne-Stokes breathing makes the breathing regular. This has been confirmed by many others. (3) Arterial blood studies of Harrison and Wilkins⁴⁰ have shown arterial CO₂-tensions "below normal" in 13 out of 18 patients investigated.

That CO₂ deficiency is not essential to the initiation of Cheyne-Stokes respiration is proved by the observations viz., (1) The CO₂ tension of arterial blood has been found to be normal or even above normal in some cases of this type (e.g., in 8 of the 18 cases studied by Harrison and Wilkins)⁴⁰. (2) The CO₂-tension of arterial blood is often raised rather than lowered in cases of Cheyne-Stokes breathing secondary to overdose of morphia.

3 *Diminution in the Irritability of the Respiratory Centre*—There is no doubt that this factor plays a dominant or major role in the causation of some cases of Cheyne-Stokes respiration. The role of this factor has been proved by the following observations: (1) Periodic breathing tends to appear, in normal individuals, especially in children and in the elderly, at the onset of sleep, when the sensitivity of the C N S is in abeyance. (2) The frequency of period of breathing, both in man and animals, after large doses of morphia. (3) The great frequency of periodic breathing in animals during hibernation has been reported. In Harrison's⁶¹ experience, periodic breathing is more common "during the intermediate state between sleeping and waking", being not related" so much to the sleeping or waking states, but to the transition in either direction between these two states."

4 *Cerebral Ischaemia or Reduction in Cerebral Blood-flow*—This has been suggested, as a possible aetiological factor, in a certain percentage (only) of cases of Cheyne-Stokes respiration, mainly on the following evidence viz, (1) Greeley and Greeley⁴⁷ were able to produce Cheyne-Stokes respiration in morphinized dogs, by artificially reducing the cerebral blood-flow. (2) Cheyne-Stokes respiration in hypertensive subjects, as shown by Fishberg,⁴⁶ occurs more often in the later stages of the disease, when heart-failure has resulted in a lowering of arterial blood-pressure with consequent reduction of blood-supply to the brain.

5 *Intermittent blood-supply to the Respiratory centre (Eyster's theory)*^{35, 36}—According to Eyster, the operation of such an intermittent blood-supply to the respiratory center depends on "rhythmic undulations of blood-pressure above and below the level of a raised intracranial pressure."

This theory has been supported by the following observations viz, (1) Uhlenbruck¹¹⁷, Carnot, Carole and Freher⁴⁰ and Fishberg⁴⁰ have succeeded in abolishing Cheyne-Stokes breathing in some cases, by simply removing some C S F by lumbar puncture, in order to lower the intracranial tension. (2) High C S F pressures have been reported by Fishberg,⁴⁰ and by Harrison⁶² in cases of high blood pressure and of cardiac failure. (3) A parallelism between venous pressures and intracranial pressures has been observed e.g., in cases of cardiac failure.

6 *Diminished Velocity of Circulation or Increased Circulation Time (Klein's Theory)*⁷²—According to Klein^{72, 61} it is the diminished velocity of circulation, in cases of heart-disease, that is responsible for Cheyne-Stokes respiration, at least in a fair percentage of cases. His theory has not been proved as yet.

7 *Increasing Pulmonary Congestion (Harrison's Theory)*⁶¹—According to Harrison,⁶¹ an increasing pulmonary congestion during the crescendo phase, may be of some pathogenetic importance in cases of Cheyne-Stokes breathing. In his view, the train of events, in such cases, may be somewhat as follows, viz, (1) During the early phases of hyperpnoea, the respiratory movements bring about an increased venous inflow and hence increasing pulmonary congestion. (2) The increasing congestion stimulates the respiration, through the intermediation of the Hering-Brauer reflex. (3) Because of the hyperventilation washing out the CO₂ from the blood, the respiratory centre becomes depressed with resultant apnoea. (4) During apnoea, oxygen-lack keeps on increasing until it is sufficient enough to stimulate the respiratory centre, thus restarting the whole cycle.

Theories of the mechanism of C S respiration—(1) Cheyne's and Stokes Theory (1818-1854) The Dublin physicians, Cheyne¹³ and Stokes¹¹³ who were responsible for familiarizing the profession with the entity of C S breathing behaved the condition to be characteristic of faulty degeneration of the heart. This theory is of historical interest only.

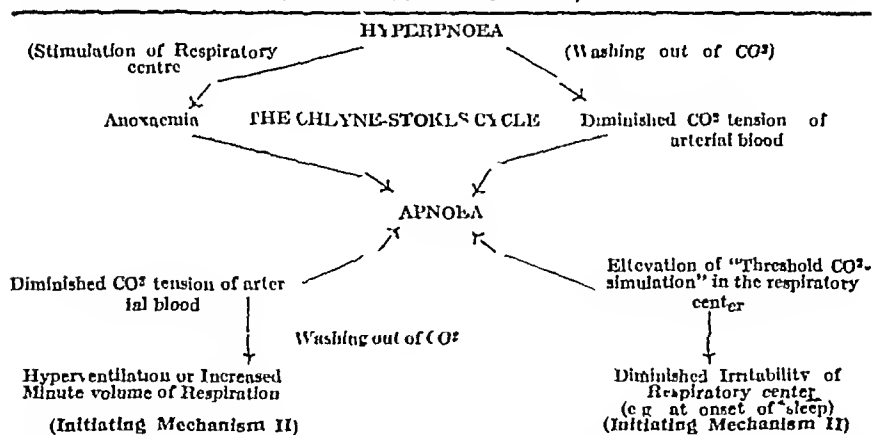
(2) *Traube's Theory*¹¹⁶—(1870) Traube¹¹⁶ ascribed C S breathing diminished supply of oxygenated blood to the brain, the CO_2 lack was said to lead to diminish irritability of the respiratory centre and apnoea, during apnoea CO_2 accumulated in the blood and stimulated deep respiration, during the deep respiration, CO_2 being washed out of the blood, the respiratory stimulus was removed and apnoea returned.

(Diminished cerebral blood supply) \rightarrow O_2 lack to Resp centre \rightarrow Diminished Irritability of Resp centre \rightarrow apnoea
 apnoea \leftarrow Washing out of CO_2 from blood \leftarrow Hyperpnoea for Res Stimulation \leftarrow accumulation of CO_2 in blood

(3) *The present-day theory* (based on the pioneer investigations of Douglas and Haldane²⁹ and Harrison⁵¹ and others)

According to Fishberg⁴⁰, the most important factor to remember about C S respiration is that the "lead" in the chemical regulation of respiration is transferred from CO_2 to O_2 . Under normal conditions of life, chemical regulation of respiration is managed by the CO_2 of the blood but in Cheyne-Stokes breathing, CO_2 and not O_2 becomes the regulator of respiration (as shown by Haldane and others⁵⁰). This is brought about as shown in Table 6.

TABLE VI
 DIAGRAM THE PHYSIOLOGICAL MECHANISM OF CHEYNE-STOKES BREATHING
 (BASED ON THE PIONEER INVESTIGATIONS OF HALDANE, DOUGLAS, 29,
 HARRISON AND OTHERS 51)



The following details will explain this difficult diagram. It is usually one of the following two mechanisms which initiates Cheyne-Stokes breathing in the majority of cases.

*Initiating mechanisms*⁵¹

(1) Over ventilation, hyperventilation or increased minute volume of respiration. This will result in a "washing out" of CO_2 from the blood. As a result there is a diminution in the CO_2 -tension of arterial

blood. If the diminution in CO_2 tension be severe enough or if it be severe enough or if it be not neutralized by an increase in CO_2 from "impairment of CO_2 diffusion through pulmonary membrane" (the so called "preventing mechanisms") then the respiration centre is no longer stimulated by CO_2 and apnoea results.

(2) Another initiating mechanism (which plays a part especially in cases of C S respiration seen after morphia poisoning and at the onset of sleep) is "depression of the irritability" or "depressed sensitivity" of the respiration centre. Such depression will raise the threshold for stimulation of the Respiration centre by CO_2 . As a result of this, even normal CO_2 tensions are rendered incapable of stimulating the respiration centre and apnoea results.

While in the case of the first initiating mechanism (over ventilation) there is an "active diminution of CO_2 " in the second mechanism the lack is "passive" and due to an elevation of the CO_2 threshold. In either case, it is disturbance of CO_2 that initiates of C S respiration.

The Cheyne-Stokes cycle

(1) Once apnoea arises (either as a sequel to hyperventilation or to diminished irritability of the respiration centre), the continuance of that state induces two chemical changes in arterial blood.

1. A diminution in the O_2 tension (or anoxaemia).

2. An accumulation of CO_2 .

(2) It has been shown that though both these alterations are capable of stimulating the respiration centre, in actual practice, it is the anoxaemia, rather than the CO_2 accumulation which stimulates the respiratory centre and induces hyperpnoea.

(3) The increased respiration again washing out CO_2 from the blood which in turn induces apnoea and continues the cycle.

Arresting mechanisms—This cycle would continue *ad infinitum* but for the fact that with each succeeding apnoeic phase, the CO_2 tension of arterial blood mounts and finally becomes severe enough to reach the threshold for the respiration centre and induces continuous respiration on its own.

Differences in sensitivity of Respiration centre to O_2 and CO_2 alterations. According to Haldane⁵⁰ the respiration centre reacts quickly to alterations of O_2 tensions in blood and comparatively slowly (with "inertia") to alterations in CO_2 tension. As a result, when CO_2 is the chemical regulator of respiration, the latter process is "smooth" while in cases where oxygen lack takes the "lead" in the chemic regulation of respiration, the latter becomes jerky (like "a steam engine without a fly wheel").

(4) *Eyster's Theory*^{35, 36, 40}—(Probably holds for a minority of cases only, especially in cases accompanied by increased intracranial tension). According to him, the governing factor in these cases is the oscillation or rhythmic undulation of the blood pressure above and below the level of the intracranial tension.

Evening Dyspnoea—This type of respiratory distress has been both described and named by Harrison and associates⁵¹. It is a type of dyspnoea that comes on gradually in the evening hours, in heart cases, and tends to prevent the patient from falling off to sleep. Unlike paroxysmal dyspnoea, evening dyspnoea arises gradually rather than suddenly and occurs during the waking hours and not during sleep.

Evening dyspnoea, although observed occasionally in cases of mitral stenosis, is particularly common in cases of left ventricular failure i.e. from high blood pressure, aortic diseases and coronary artery disease

Pathogenesis—The following factors have been incriminated in the genesis of this variety of dyspnoea, viz

(1) *Increased pulmonary congestion in the evening hours*⁵¹—This has been ascribed to increased metabolic activities of the evening hours (an increase of about 10 per cent) with corresponding increase of blood-supply to the organs and hence an increased venous-return to the heart with raised cardiac output (of the right ventricle). If the left ventricle happens to be less efficient than the right, excess of blood in the lesser circuit will induce a state of pulmonary congestion. According to Harrison,⁵¹ even if the right ventricle were to pump just 1/30th of a drop more blood, at each heart beat, than the left ventricle enough pulmonary congestion would develop within twelve hours to cause dyspnoea.

The increase in pulmonary congestion, towards evening, leads to (1) increase in ventilation. In Harrison's series of cases,⁵¹ the ventilation increased by about 15 per cent in the evening hours, the values for morning and evening hours being 8.4 and 9.7 litres respectively. (2) A reduced vital capacity. Harrison⁵¹ found an average reduction of about 8 per cent.

Because of the association of these two factors, there is a rise of the "resting ventilation ratio",⁵¹ by about 25 per cent, during the evening hours, (the average figures being 8.8 for morning hours and 4.2 for evening hours). This, in turn, leads to dyspnoea.

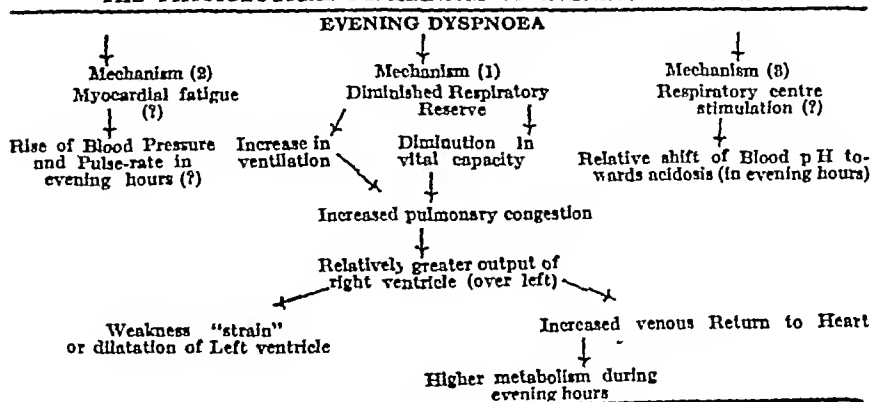
Evening dyspnoea is more common in cardiac patients who remain ambulant, this is so, because the effort of moving about leads to greater venous return and hence to greater pulmonary congestion in the evening hours.

(2) *Evening acidosis*—A shift of the reaction of the blood acid, (in the evening hours), as the result of increased metabolic activity, has also been suggested as a possibility.

(3) Increased work on the part of the heart, has also been suggested as a possibility, partly from the rise of arterial blood-pressure and partly from the tendency to tachycardia, towards evening hours.

The physiological mechanism of evening dyspnoea, is presented, in diagrammatic form, in table 7.

TABLE VII
THE PHYSIOLOGICAL MECHANISM OF EVENING DYSPNOEA



Dyspnoea of Complications—Dyspnoea may arise, in cases of heart disease, as a secondary manifestation, i.e. secondary to the accumulation of fluid in one or other of the serous sacs. As a rule, these complications arise along after the actual inception of dyspnoea and play a subsidiary role only.

For the physiological mechanisms of dyspnoea in cases of hydrothorax and pericardial effusion the reader is referred to Fig 8 and 9. The figures are self-explanatory.

TABLE VIII

THE PHYSIOLOGICAL MECHANISM OF DYSPNOEA IN CASES OF HYDROTHORAX

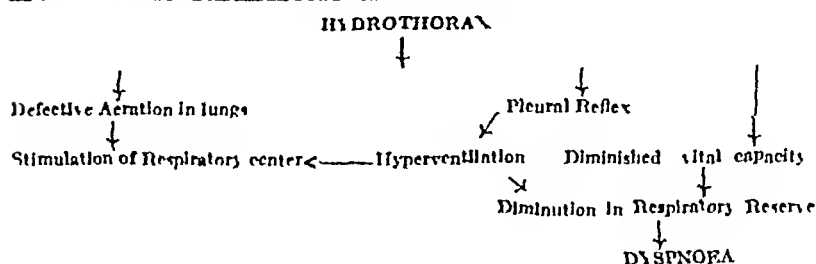
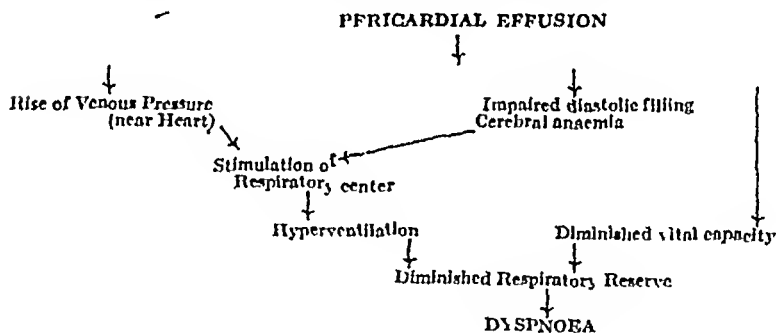


TABLE IX

THE PHYSIOLOGICAL MECHANISM OF DYSPNOEA IN CASES OF PERICARDIAL EFFUSION



Psychogenic Dyspnoea—This usually takes the form of the so called "sighing respiration" or "suspicious breathing". Lately, brought into prominence by the able investigations of Doris Baker^{1a}, this entity or disorder of breathing is frequently mistaken for genuine or organic cardiac dyspnoea.

This condition had been briefly mentioned in the last century, by both Walshe^{1a} and Gairdner^{43a}, under the designation of "suspicious respiration". Whilst Walshe^{1a} preferred to regard it as a variety pseudo-angina, Gairdner^{43a} attributed it "to lesions involving the respiration through the cardiac nerves". Mund and Wasserman^{87a} (1927), after a full investigation of this symptom, came too regard it as a mild form of cardiac dyspnoea, a reaction to a mild form of insufficient oxygenation of the blood. Paul white and Hahn^{124a} (1929), came to the conclusion that this condition, particularly in women in the twenties, is a symptom of "neurosis" secondary to any disease of the heart, lungs,

Gallavardin^{44a} (1938) has referred to a "functional diaphragmatic defect", an unusual respiratory disorder of nervous origin, quite distinct from true dyspnoea and noted more often at rest than during exertion

The condition has variously been described in the literature as "suspicious respiration", sighing, deep sighing, respiration, "irregular sighing respiration," difficult inspiration, difficulty in taking a full breath", inadequate breathing and even as a "struggle for breath"^{1a}

Pathogenesis—The pathogenesis of this fairly common clinical entity remains obscure, although it is commonly associated with symptoms of neurosis or physical exhaustion Doris Baker,^{1a} after a study of it, suggests its possible association with diaphragmatic spasm and regards it as a neurosis symptom "in no circumstances an indication of cardiovascular disease"

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Critical Notes and Abstracts

RENAL PTOSIS AND ITS TREATMENT

Discussing renal ptosis and its treatment, William F Braasch et al state that the condition occurs most frequently in thin underweight women and most commonly affects the right kidney. It may appear in large numbers of persons without causing symptoms of pathology. Subjective symptoms may be variable and ill-defined and an uncertain guide in diagnosis. Borderline pyelocaliectasis and the so-called flabby pelvis is found associated with renal ptosis. In 21 of the patients discussed one underwent nephropexy, 11 patients were subjectively benefited and 10 patients were apparently not benefited by operation. Only three of those benefited had permanent relief. In the other eight patients original complaints of pain were relieved but other symptoms continued.

The authors consider that most patients with anephroptosis can be benefited by nonoperative measures. Even though evidence of delayed renal drainage, such as borderline pyelectasis and retained medium as observed in the delayed urogram, may not necessarily indicate obstruction, nephropexy is advisable only when such evidence of obstruction is present. The authors consider that a conservative attitude toward this condition is substantiated by the fact that many patients observed at their clinic have previously undergone nephropexy elsewhere without relief of symptoms.

(Braasch, William F., Mayo Clinic, Rochester, Minn.; Greene, Laurence F., and Goyanna, Huy "Renal Ptosis and Its Treatment" J. A. M. A. 188: 399-403 October, 1948)

ASSOCIATION BETWEEN GASTRIC ACHLORHYDRIA AND SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

Spies et al., reporting on a two-year survey on the effect of synthetic folic acid in persons with macrocytic anemia confirms and extends previous observations that folic acid is an effective antianemia substance capable of producing a clinical response and hematologic remission of macrocytic anemia, tropical sprue, and the macrocytic anemia of pellagra and pregnancy. The study shows however that folic acid does not prevent neural disturbances.

Twenty-eight of the 38 cases in this study who were observed over a period of two years developed sub-acute combined degeneration irrespective of how much folic acid was administered. Following massive liver extract therapy, it was promptly relieved. In contrast to persons with Addisonian pernicious anemia, those with nutritional macrocytic anemia, tropical sprue, and the macrocytic anemia of pregnancy in this series did not have histamine refractory achlorhydria either previous to or during therapy with folic acid and in no instance did any evidence of subacute combined degeneration develop.

Spies supports the concept that vitamin deficiencies in human beings tend to be multiple in nature. The administration of a specific vitamin corrects for a deficiency of itself and often aids in improving the general health and well-being of the patient but it cannot correct a deficiency of all of the essential dietary nutrients. In another series of three patients with achlorhydria, Addisonian pernicious anemia, and subacute combined degeneration of the spinal cord, all volunteered relief of symp-

toms following the parenteral injection of 15 micrograms of vitamin B12. The subjective improvement in all three cases was considered remarkable and in the case which was most acute there was considerable improvement in physical signs.

(Spies, Tom D. Northwestern University, Chicago, Ill. Stone, Robert E.; Lopez, Guillermo Carcia; Milanes, Fernando; Aramburu, Tomas; and Toca, Ruben Lopez: 'The Association Between Combined Degeneration of the Spinal Cord.' Postgraduate Medicine 4:80 05 August, 1948)

URETHANE IN LEUKEMIA—(HADDOW, A., and SEXTON, W. A. Influence of Carbamic Esters (Urethanes) on Experimental Animal Tumours, *Nature*, London, 157:500, 1946)

Urethane (ethyl carbamate) belongs to the group of organic esters of carbamic acid. Although the whole group of esters are designated as urethanes, the term has generally been limited to ethyl carbamate. Urethane is closely related chemically to urea and carbomal. The drug was synthesized in 1834, but until recently it has been used chiefly as a laboratory anesthetic. Its hypnotic action in man is feeble, but it is rapid and potent in animals. Because of its feeble and uncertain action, it was used only briefly as a hypnotic in humans. Combined with quinine hydrochloride it has been used as a sclerosing solution for the injection treatment of varicose veins. Haddow and Sexton have reviewed the experimental work leading to the recent trial of urethane in the treatment of malignant growths, which led to the discovery that it induced remissions in patients having leukemia. They were unable to determine the mode of action of urethane but concluded that it is reasonable to suspect that the drug may act on growth primarily through the processes of maturation and in leukemia by tending to remedy some deficiency in these processes.

Experimental and Clinical studies—Paterson, Thomas, Haddow, and Watkinson reported the clinical results leading from the work of Haddow and Sexton. They decided to try urethane in the treatment of leukemia of finding that there was a fall in the leukocyte count in some cases of advanced malignant disease treated with urethane. They found that although normal white cells are susceptible to the action of urethane, they are relatively much more refractory than are leukemic cells. Urethane was used in thirty-two cases of leukemia (nineteen myeloid and thirteen lymphatic) observed over periods ranging between eleven months and five weeks. "The effects produced represented in the most favourable cases by a fall in total white cells count to normal limits, a tendency for the differential count to approach a more normal pattern, diminution in size of the spleen and enlarged lymph nodes, and a rise in hemoglobin—are remarkably similar to those obtained by standard methods of deep X-ray therapy." There was no indication that permanent benefit may result from the use of urethane in either myeloid or lymphatic leukemia.

Beddinger, Pocher, and Limarzi (Effect of Urethane on Leukemia, *J Lab & Clin Med*, 32:1894, 1947) concluded that urethane in oral doses of 1 to 5 grams daily will produce moderate to marked fall in the leukocyte count in patients with acute leukemia, although there is little or no clinical improvement. In patients with chronic lymphatic leukemia and chronic myeloid leukemia, there is a tendency for the blood pattern to approach a more normal pattern with a tendency in size of the lymph nodes and spleen. They induced by the drug in chronic

following roentgen therapy, and that there is no indication that urethane has any permanent effect on the leukemic process

Hirschboeck, Lindert, Chase, and Calvy (Effects of Urethane in the Treatment of Leukemia and Metastatic Malignant Tumours, J A M A, 186-90, 1948) were of the opinion that urethane appears to be of little or no benefit in producing remissions or prolonging life in acute leukemia, although severe leukopenia was produced in most of the patients. Its action in chronic lymphatic leukemia was variable, but, when effective produced results comparable to those obtained with roentgen therapy. It was most consistently successful in controlling chronic myelogenous leukemia. They consider the drug to have the following advantages: ease of administration and regulation of dosage, a minimum of toxic side actions, a desirable sedative effect, and low cost.

Forker, Jacobson, Osgood, and Dameshek in discussing the paper presented by Hirschboeck et al., agreed that urethane produces temporary improvement in patients having chronic myelogenous leukemia but felt that the improvement probably is not as great as that following X-ray therapy.

Webster, J J (Urethane in Leukemia J A M A 135-901, 1947) reported a fatality in a case of myelogenous leukemia after treatment with urethane. He concluded that urethane, apparently non-toxic in normal beings, is a selective mitotic inhibitor which has its principal action in leukemia on early myeloid cells. He believed that urethane has a place in the treatment of leukemia but that continued investigation is necessary to ascertain proper procedure, dosage, toxic levels, and mode of action before widespread use is advocated.

Method of Administration and Dosage—Urethane has been prescribed in a solution of chloroform water and syrup of orange, 1 in simple syrup, 2.5 0.5-Gm gelatin capsules, 8 and 0.5 and 0.8-Gm enteric-coated capsules and tablets, 2.8 and in 40 and 50 per cent solutions intramuscularly. Gastric irritation, as evidenced by nausea and vomiting, was to a great extent obviated by the use of the enteric-coated tablets. The usual recommended dose is one gram three times daily, but the dose has varied from one to six grams daily. Length of continuous treatment has varied from two days to six months. Paterson et al. stated that the dosage was determined by the tolerance of the patient and by the rate of drop of the white cell count. The amount of urethane necessary to produce a fall to about 20 000 white cells per cubic millimeter varied within wide limits (from 19 Gm to 184 Gm). It is recommended that the drug be discontinued when the white count is reduced to 20 000 per cubic millimeter. It can then be resumed when indicated by the clinical condition of the patient and the white count. Attempts at reducing the white count to normal and at returning the spleen to normal size may result in disaster inasmuch as fatal agranulocytosis may be produced. Transfusions are usually required as indicated by clinical condition of the patient as supplemental treatment to the urethane.

Urethane has not been used over any extended period of time in the treatment of human beings. Jaffe, W G (Carcinogenic Action of Ethyl Urethane on Rats, Cancer Research, 7 107, 1947) however, has found increased incidence of pulmonary adenomas and malignant hepatomas in rats receiving prolonged administration of urethane and has warned that this might occur in human beings.

Conclusions —Urethane may be considered as an additional therapeutic agent available in the treatment of the leukemias. It, like all the other ones heretofore put forward, has no permanent effect on the leukemic process. It is most effective in the treatment of chronic myelogenous leukemia, is a little less effective in the treatment of chronic lymphatic leukemia, and is not effective in the treatment of acute leukemia. Although it is not a cure for leukemia, the study of its action may help to elucidate the mechanism of white-blood-cell regeneration and destruction, this we must know before we can hope to influence successfully the fatal disease of unknown cause, leukemia.

EMETINE TOXICITY IN MAN

Studies on the nature of early toxic manifestations, their relation to the dose level and their significance in determining safe dosage during emetine therapy are reported by Klatskin and Friedman. Toxic manifestations are common in the therapeutic dose range of emetine, and may occur at any dose level depending on individual susceptibility to the drug. Emetine is a general protoplasmic poison with a predilection for muscle, and possibly nerve, tissue, not only of the heart, but also of the vascular, gastrointestinal and skeletal systems. This is reflected in the multiplicity of manifestations that appear once toxicity occurs.

The manifestations of emetine toxicity fall into four groups: local, gastrointestinal, cardiovascular and neuromuscular. The local reaction occurs in all but a few patients when emetine is given subcutaneously. Generalized weakness, electrocardiographic changes and diarrhea occur in approximately half the subjects, and the incidence of the other toxic manifestations varies between 5.4 and 35.5 per cent. The local reaction appears to be due to a myositis in many cases. The diarrhoea induced by emetine is due to increased peristalsis. With very large doses ulceration of the mucosa may occur, although this has never been demonstrated in man. The nausea and vomiting are probably of central origin when the drug is given parenterally. Emetine produces changes in the myocardium, as evidenced by the appearance of electrocardiographic abnormalities, but the other cardiovascular manifestations of toxicity seen in man are usually not cardiac in origin.

The clinical features of emetine "neuritis" are usually those of a myositis. If a true emetin neuritis occurs in man it must be rare. Although the effects of multiple doses of emetine are cumulative, many of its toxic manifestations subside during treatment, suggesting that some degree of tolerance may be acquired. Electrocardiographic abnormalities and "neuritis" rarely regress unless treatment is stopped, so that their appearance is an indication for immediate withdrawal of emetine. The other signs of toxicity, however, need not contraindicate further treatment unless they increase in severity or fail to subside in a day or two.

The toxic effects of emetine are reversible if the drug is stopped early enough. Most of them clear up in a few days, but electrocardiographic changes and "neuritis" may persist for weeks. There may be a latent period between the cessation of emetin therapy and the appearance of electrocardiographic abnormalities and signs of "neuritis". Patients should, therefore, be watched for

weeks following treatment. Relatively large doses of emetine can be given with safety, provided treatment is interrupted by rest periods adequate to compensate for the cumulative effects of the drug.

(Klatzkin, Gerald. Department of Internal Medicine, Yale University School of Medicine, New Haven Conn. and Friedman Harry: *Emetine Toxicity in Man: Studies on the Nature of Early Toxic Manifestations, Their Relation to the Dose Level, and Their Significance in Determining Safe Dosage*. *Annals Int. Med.* 28:892-915 Mar. 1948.)

CHANGE IN FLUID BALANCE MAY KILL MALARIA VICTIMS —(Science News Letter, May 22, 53-822, 1948)

A contributing cause of death in malaria may be a change in fluid balance in the body and not the malaria germs themselves. Studies with monkeys and humans suggesting this were reported by Dr. Richard R. Overman of the University of Tennessee College of Medicine.

The same condition may be the cause of the debility after an attack of malaria, Dr. Overman thinks.

During the attack of malaria, he finds, the walls of the body's cells become more permeable. Substances get inside the cells which normally should not be there. Dr. Overman believes the intermittent fever of malaria is what makes the cell walls permeable. The same thing may happen, he suggests, in other diseases with fever that comes and goes.

The cells permeability can be reversed by treatment with anti-malaria chemicals. But if the condition becomes serious enough, it is no longer reversible. This was the case in monkeys, and Dr. Overman believes it also occurs in humans. Monkeys given anti-malarial chemicals after the fluid upset had become serious died, though the chemicals had killed all the malarial parasites.

THE SIGNIFICANCE OF GIANT FOLLICULAR LYMPHADENOPATHY —(E. M. Uhlmann, Chicago, Ill. *Radiology*, February 1948, 50,147-157)

The condition known as giant follicular lymphadenopathy and associated with the names of Brill and Symmers, is a disease of the lymph nodes which has attracted increasing attention during the past few years. It seems that this disease, while not uncommon, is still little known among the medical profession in general, and often is not correctly interpreted by pathologists, it offers many challenging aspects to the internist, the surgeon, the hematologist, the pathologist, and the therapist.

The disease bears a strong resemblance to Hodgkin's disease and in most instances is diagnosed as such. Giant follicular lymphadenopathy is characterized by either localized or generalized enlargement of the superficial lymph nodes, often in conjunction with splenomegaly. The first enlargement seems frequently to be in the lymph nodes of the neck, but there is no preference for any particular site. Lymph node swelling may occur in the supraclavicular fossa, in the axilla, in the groin, or in the abdomen, or may be generalized, involving practically all palpable lymph nodes of the body. The involved nodes are usually rather soft, only very seldom do they become hard. Their size may vary from a chain of small lymph nodes to masses as large as a grapefruit, without any regularity. The lymph nodes may remain unchanged in size or configuration for months or even years, but in other instances the occurrence of a single lymph node is quickly followed by generalized lymphadenopathy. The general condition of the patient is usually not

influenced to any extent by the lymphadenopathy, even if generalized. Enlargement of the spleen is a rather common feature of the disease. Pain is practically never present, and there are no characteristic alterations in the peripheral blood.

While there is no age limit for giant follicular lymphadenopathy, those in the third and fourth decades seem to be afflicted more frequently than younger or older persons. There is no definite sex preference.

The microscopic findings in the lymph nodes are rather characteristic and should not be mistaken for leukemia, sarcoma, or Hodgkin's disease. In most instances the anatomic structure of the lymph follicles is changed, but not completely destroyed, and for this reason most pathologists, if they are not thoroughly acquainted with the characteristics of the disease, are hesitant to make a diagnosis of a malignant lesion. Chronic lymphadenitis and lymphoid hyperplasia are the most frequent terms used by pathologists to describe the microscopic findings. The histologic changes are comparatively simple, and consist, as Symmers has aptly stated, of numerical and dimensional hyperplasia of the lymph follicles. Frequently, these follicles are difficult to distinguish from the familiar hyperplasia which occurs with innumerable inflammatory conditions, and not uncommonly also with benign and malignant neoplasms. Often the follicles are filled with large hypochromatic or even achromatic nuclei, also called "shadow cells," of various shapes. In some instances the peripheral zone of small lymphocytes is absent, while in others the follicles may be made up exclusively of small lymphocytes. As long as these cells remain localized within the lymph follicles, the disease must be diagnosed as giant follicular lymphadenopathy, but rupture of the follicles with escape of the cells into the surrounding tissues of the lymph node is usually considered to be pathognomonic of polymorphous-cells sarcoma.

It is an established fact that the disease, seemingly of the benign nature, can develop into a true malignant condition, such as leukemia, sarcoma, or Hodgkin's disease. The most interesting fact to us is that any one of these three diseases may follow the original giant follicular lymphadenopathy, and this may be taken as another sign of the close relationship between these different forms of the so-called lymphoblastoma. Furthermore, while we agree that small amounts of radiation will be sufficient in most instances to produce the disappearance of the involved lymph nodes, we do not believe, that if giant follicular lymphadenopathy is treated with large amounts of radiation, such as are commonly used in the treatment of malignant lesions, the patients will remain free of symptoms for many years. Judging from our experience, it seems to be logical to treat giant follicular lymphadenopathy from the very beginning as a potentially malignant disease, regardless of the fact that the microscopic findings may not warrant that diagnosis. In our opinion the clinician, should prevail over the pathologist and insist on intensive therapy which may control the symptoms and prevent the development of Hodgkin's disease, leukemia, and sarcoma.

STREPTOMYCIN TREATMENT OF PERTUSSIS—The organism *H. Pertussis* is extremely sensitive to streptomycin. However, it has been found that the administration of streptomycin by parenteral means fails to control the disease. For this reason, a number of investigators have used streptomycin aerosols in an attempt to produce high concentrations at the site of the infection. From the preliminary reports, it would appear that this mode of administration is most successful in treating pertussis. Nebulizers should produce mists of particles varying from 2 to 5 microns in diameter. The usual dosage schedule for infants is 25,000 units every three hours. For older children, 50,000 units may be administered in the same fashion, since little or no streptomycin is absorbed systematically when this mode of administration is used, toxic reactions rarely occur.

Streptomycin aerosol therapy in the home may be accomplished with the use of either a manually operated nebulizer or compressed oxygen. Infants and very small children may require the use of a face mask or a small oxygen tent.

PREVENTION AND TREATMENT OF PLAGUE—RUESEGGER, J. M. and GILCHRIST, H. Plague. A survey of Recent Developments in the Prevention and Treatment of the Disease, *Am J Trop Med* 27 683, 1947).

In the prevention of plague, quarantine isolation, destruction of the animal reservoirs and insect vectors, immunization, and the use of chemotherapy are the methods that can be used.

Animal reservoirs are vulnerable to attack, and the introduction of raticidal drugs raised hopes that plague might be abolished. However, such programs are subject to technical difficulties which usually defeat the main purpose. The experience of workers in the western United States would lead one to believe that the complete elimination of rats would not entirely solve the plague problem, the intermediate vector is apparently able to adapt its parasitic life to other rodents or even avian hosts. Destruction of the fleas is thus considered by some workers the most practical approach to plague control, especially once an epidemic is imminent or in progress. The pulicidal efficacy of DDT invariably has been confirmed.

Use of vaccines and anti-plague serums has been effective, although it has offered some difficulties. The United States Army used a formalin-killed, agar-grown suspension of virulent plague bacilli in carbolyzed saline. The fact that not a single infection with *Pasteurella pestis* occurred in the vaccinated group, despite probably exposure in many areas, is suggestive of the preventive action of the vaccine. Establishment of passive immunity through anti-plague serum has been effected but the short duration of this type of immunity makes it impractical. The value of serum as a specific therapeutic agent in plague is unquestionable, but technical difficulties in the production of a potent serum have prevented its popular use.

Lately, some observations have been made in which sulfadiazine and sulfathiazole apparently prevented the appearance of the disease in a large number of contacts and in laboratory workers following accidents in the laboratory.

The sulfonamides appear to be the most effective therapeutic agents in plague, suggestive confirmation of their curative effect in human infections is accumulating. In one epidemic area, the case

fatality rate in a series of patients treated with sulfadiazine and sulfathiazole was 20 and 37 per cent, whereas under other type of treatment it was in excess of 90 per cent. The recovery of three cases of pulmonary plague has also been reported.

Recently, in China, a physician developed plague pneumonitis while working in his laboratory. Sulfadiazine therapy was instituted on the second day of symptoms after the diagnosis had been confirmed culturally. On the fourth day, and for several days thereafter, streptomycin was also administered. The fact that the patient made an uneventful and complete recovery bore out the prediction implied in previous experimental work. The possibility of combined therapy, with resultant potentiation of therapeutic action requires clinical trial.

THE TREATMENT OF *E. COLI* URINARY INFECTIONS WITH SULFATHALIDINE (PHthalylSULFATHIAZOLE)

In a previous study on the treatment of *Escherichia coli* infections of the urinary tract, the poorly absorbed sulfonamide, 'Sulfasuxidine' succinylsulfathiazole, was found to be an effective bacteriostatic agent in rendering the urine sterile. Infections resistant to other sulfonamides were cured, and the drug was tolerated well by patients who were sensitive to other sulfonamides or who seemed likely not to tolerate these drugs because of renal dysfunction or anemia.

The present study reports the results obtained in treating *Escherichia coli* infections of the urinary tract with another poorly absorbed sulfonamide, 'Sulfathalidine' (phthalylsulfathiazole), which exerts its anti-bacterial action in a dosage one third to one-half that commonly used with 'Sulfasuxidine' succinylsulfathiazole. Since the daily urinary excretion of phthalylsulfathiazole is approximately 5 per cent of the amount administered on a dosage of 1 Gm. four times a day, the concentration of each of the drugs excreted in the urine (free sulfathiazole and combined phthalylsulfathiazole) is calculated to be approximately 6 Gmg. per 100 cc., assuring an average daily urine output of 1,500 cc.

Fifty patients with *E. coli* infections of the urinary tract received 'sulfathalidine' phthalylsulfathiazole in a daily dosage of 0.1 Gm. per kilogram of body weight (usually 4 Gm.) for a period of three weeks. These infections included cystitis or pyelitis, chronic or recurring pyelitis, pyelitis or cystitis of pregnancy, and puerperal pyelitis or cystitis. Untoward reactions were not encountered even though at least one patient received the drug throughout five months of pregnancy. All but one patient obtained symptomatic relief, the urine of this one patient promptly became sterile, and it was concluded that the *E. coli* infection was superimposed on a mild interstitial cystitis. The urine of 7 patients was not rendered sterile, although all experienced symptomatic relief. Other factors such as obstructive lesions, ureteritis cystica, and the presence of a small calculus in the right pelvis were responsible for the bacteriologic failure in 6 of these patients.

In two groups of 24 and 21 patients followed for six to thirty months and two to six months, respectively, a bacteriologic cure was obtained in a total of 34 patients (75.5 per cent) and symptomatic cure in 39 (86.6 per cent). Late recurrences of infection were treated successfully in 6 of 7 patients by a second course of the drug. Phthalylsulfathiazole like succinylsulfathiazole, has the advantage of being effective when administered to patients who have tolerated other sulfonamides poorly, particularly sulfadiazine and sulfathiazole, or who have not been treated

successfully with these drugs. Of 22 such patients, an immediate cure with phthalylsulfathiazole was obtained in 16 or 72.7 per cent, and a late cure in 14 or 63.6 per cent.

The immediate effects of 'Sulfathiazidine' phthalylsulfathiazole and 'sulfasuxidine' succinylsulfathiazole in urinary tract infections, it is believed, may be due to their greater bacteriostatic effect on *E. coli*, even though the concentration of these drugs in the blood and urine is lower than that of sulfathiazole and sulfadiazine. The persistence of cure that appears to be obtained with phthalylsulfathiazole and succinylsulfathiazole is ascribed primarily to two factors. Elimination of the source of infection from the bowel may protect the tissues of the urinary tract against recurrent infection by affording opportunity to develop natural resistance. The bacteriostatic effect of the drugs on organisms of the bowel may also block the escape of these organisms into the urinary tract. Therefore although the urine is rendered sterile and an immediate cure is effected in most patients when phthalylsulfathiazole is administered for less than a week the drug should be given for at least two weeks and preferably three weeks to prevent recurrence of infection.

THE TREATMENT OF HYPERTENSION—(J A M A November 1, 1947, 135:576-577)

For the past two years patients from many parts of the United States have sought relief from hypertension in North Carolina where they followed the so-called rice diet. Some have returned with unaltered blood pressure and an intense aversion to dietary management, but many others have returned to their homes with reduced blood pressure, improved vision, smaller cardiac silhouettes and a determination to remain on a diet low in protein and salt.

A recent study confirms older work on the use of a low salt regimen for heart failure and hypertension. A diet with 200 mg of sodium and 70 Gm of protein per day led to a fall of 20 mm of mercury or more in the diastolic pressure of 58% of ambulatory patients who stayed on the diet for weeks or months. The best results reported for splanchicectomy showed a similar fall in 61% of the cases. Physicians should test the value of sodium depletion, without protein restriction, in any hypertensive patient whose disabilities seem to warrant splanchic section.

Splanchnic section has an operative mortality and a considerable post-operative morbidity. Postural hypotension may be more disabling than the pre-operative symptoms. Sodium depletion also has a morbidity and even a mortality. Weakness, nausea and muscle cramps may ensue before a satisfactory fall in pressure has occurred. In cases with severe retinal and renal vascular disease uremia may be precipitated, it may occur even though the rice diet, with its low protein content is used.

Persons who have been on the usual American diet, which contains 5 to 8 Gm of sodium (12 to 20 Gm of salt) must follow the low salt regimen for weeks before its effect on blood pressure can be evaluated. Since patients with severe vascular disease or chronic nephritis may lose 600 to 800 mg of sodium in the urine alone as against 40 mg lost by others with hypertension, a state similar to Addison's disease occurs when the salt intake is reduced. Not only the patient's symptoms but the blood urea level must be followed carefully at the start of a regimen of sodium depletion for chronic hypertension with vascular damage.

Reiser and Burch, using radioactive isotopes, have confirmed earlier evidence that mercurial diuretic results in a net loss of sodium. The sodium diuretic precedes water diuresis by two to four hours and sodium excretion per day may be increased sevenfold while water excretion is merely doubled. In patients with hypertension and in instances of heart failure with pulmonary edema but without peripheral edema, mercurial diuretics may be helpful in hastening the loss of sodium or in permitting a somewhat more liberal diet. One dose of a mercurial diuretic may rob an edematous patient of 4,000 mg. of sodium and in edema the total loss in a week of such a dose may be 15,000 mg. Thus, a restriction of a mercurial compound in a week can more than make up for the difference in salt obtained from a rice diet and from one with a wider choice of unaltered food.

In most cases hypertensive patients with normal blood urea level can be safely tried on sodium depletion, a rice diet and mercurials for three weeks at least and pushing the therapy, if one does not respond, until the desired result is effected or undesirable symptoms occur. If a fall in pressure does not result, dietary restriction is unlikely to have any value for that patient, if the pressure falls, a regimen should be worked out which will maintain the sodium depletion. Renal impairment may make protein restriction imperative, then rice should be used as the main source of calories and protein, for Sure has shown it to be 2.5 times as effective, per Gm. of protein as is a high protein diet in maintaining the growth of young animals. On no other regimen do patients come into nitrogen equilibrium at such a low protein intake. Fruit juice, rich in potassium as it passes through the digestive tract. Fruit juice, 2 or even 3 liters per day may be used during salt restriction without fear of edema as a result.

Many patients have accepted the rice diet, and many more have accepted diets made more protein and by the use of mercurial. During the war much work was done on desalting agents to aid sailors and soldiers on life rafts. More recent studies have shown that it may be possible to prepare portable emulsions of insoluble material which will take up sodium as it passes through the digestive tract. With our present diets and diuretics, the physician can determine the effectiveness of sodium depletion on symptoms and arterial pressure of any patients. This determination may well precede any recommendation for surgery.

CLINICAL EVALUATION OF TETRA-ETHYL-AMMONIUM—(G. H. YAGI, M.D., J. H. WALKER, M.D. and W. T. RABY, M.D. *SOUTHERN MEDICAL JOURNAL*, February 1948, 41:129-133).

Tetra-Ethyl-Ammonium (TEA) both as the chloride and the bromide, is a recently developed adjunctive in the study of peripheral vascular disorders. This report covers a 9-month period in which TEA compounds were used in the diagnosis and treatment of vasospastic conditions.

TEA has been shown to block nerve impulses at the autonomic ganglia, both sympathetic and parasympathetic. Its outstanding clinical effect appears to be comparable to an extensive sympathectomy. Parenteral administration usually causes an abrupt fall in systolic and diastolic blood pressure, with an increase in the peripheral blood flow as evidenced by elevation of peripheral skin temperatures.

Other effects of TEA administration include abrupt cessation of gastro-intestinal motility, with slow return. The desire to void with

bladder distension is temporarily lost. In cases of peptic ulcer it has been shown to reduce the excess night gastric secretion and acidity, and to relieve the ulcer pain.

In addition, pupils are dilated, and accommodation is lost. Patients complain of heavy eyelids or of drowsiness, of an acid metallic taste, and of a peculiar "pins and needles" sensation over the entire body. The peculiar taste and paresthesia are transient, usually disappearing in 3 to 4 minutes.

The lowest level of blood pressure drop, following administration of TEA, is reached within 5 minutes. The pressure usually returns to normal levels within 20 minutes. There is a definite postural hypotension. The effects of peripheral vasodilation reach maximum height with intravenous TEA injections in 30 to 45 minutes, and gradually return to previous levels in one to two hours. The duration of effect is somewhat longer after intramuscular injection two to six hours.

TEA autonomic blockade is an easy method both for the clinician and for the patient, in obtaining a sympathetic block. It is more reliable than paravertebral block, and is more economical than either spinal or caudal anesthesia.

The series which we studied—totalling 116 patients—includes cases of thrombophlebitis, various stages of peripheral arteriosclerosis obliterans, lymphedema, scalenus anticus syndrome, frostbite, and acute traumatic conditions with impaired circulation. We also studied cases of hypertension as a means of testing the liability of the arterial pressure. The courses of therapy varied from intensive treatment with multiple injections for a few days, to periodic injections at intervals of a few days or a week. Most patients were ambulatory.

The drug was always administered with the patient recumbent. Dosage varied from 100 to 500 mg (1 to 50 cc) intravenously, and averaged 20 mg per Kg of body weight intramuscularly in a 10 per cent solution. The average 500 mg intravenous injection took about 30 seconds. The longest period of treatment was 96 days, and the largest total amount given to one patient was 32,000 mg. None of the patients exhibited any ill effects.

Raynaud's Disease—Four patients were studied in this group. TEA in this group played a dual role. It established the degree of vasospastic element, and clarified the need of sympathectomy. It was successful in two cases in establishing what appears to be a permanent alleviation of symptoms.

Organic Obstructive Vascular Diseases—Eighty patients were studied in this group. There were 8 with Buerger's disease, and 72 with peripheral arteriosclerosis obliterans.

All eight patients with Buerger's disease exhibited definite response to TEA, even with the initial injection. Temperature rise averaged 2 to 5°C, with subsidence of pain.

The 72 patients with peripheral arteriosclerosis obliterans showed responses which were variable and were generally unsatisfactory. Seventy per cent of the group receiving evening intramuscular injections were relieved of nocturnal pain. We believe that TEA is chiefly valuable in this group as a diagnostic aid in evaluating the probable effects of sympathectomy.

Thrombophlebitis—Four patients were studied in this group. Three had a chronic deep pelvic or femoral thrombophlebitis post-partum,

The fourth had a migratory phlebitis of the great saphenous system. All showed dramatic response to TLA injections.

Frostbite—There were 5 patients in the group, 4 with frostbite of the feet and one of the hand. All exhibited classic signs of frostiness, waxiness, pallor or cyanosis, and numbness. All were given TLA intravenously. Recovery was remarkable in all cases. The frostbitten feet walked out of the hospital symptom free in from 3 to 6 days. The patient with frozen fingers was released after 24 hours. Follow up examinations in four cases has revealed no residual damage. The fifth could not be located. It is believed that severe frostbite should have TLA therapy supplemented with anticoagulation.

Acute Traumatic Conditions—Four patients were seen in this group. All received crushing injuries with extensive soft tissue damage of the lower extremities. Results in this group were generally good.

Causalgia States—Five patients were seen in this group. For diagnostic criteria we required a history of trauma and of pain out of proportion to the injury, of long duration, and not following a pattern of innervation. In these cases the first injection of TLA relieved pain temporarily. Subsequent injection in 2 patients did not, but produced relief of pain. Two others subsequently had sympathectomy with satisfactory results.

Hypertension—Our results in this group of 10 patients were encouraging, though inconclusive. TLA produced a greater average fall in arterial pressure than did sodium amylal, though of course the fall was not sustained for more than a few hours. Two patients were relieved of severe headache by TLA after the usual measures for relief had failed.

THE USE OF A HIGH FLUID INTAKE AND A LOW SODIUM ACID ASH DIET IN THE MANAGEMENT OF PORTAL CIRRHOSIS WITH ASCITIS (JONAS J. LAYNE, M.D. and F. R. SCHRAM, M.D. GASTROENTEROLOGY, December 1947, 9:703-717)

Inasmuch as a high fluid intake and a diet which is low in sodium and yields an excess of acid ash has been found effective in the relief of ascites and hepatic passive congestion in advanced heart failure, we undertook an investigation of the value of this same regimen as an adjunct in the treatment of patients with the clinical syndrome of portal cirrhosis of the liver with ascitis. In all but one of 20 patients such regimen was found of definite value in facilitating the clearing of ascites, in lessening the need for paracentesis and in relieving the mental symptoms of hepatic insufficiency.

The 20 patients in this series were carefully selected to make certain that the diagnosis of portal cirrhosis with ascitis was correct. Wherever there existed a possibility that the diagnosis might have been confused with abdominal carcinomatosis, chronic peritonitis, or a cardiac or renal lesion, such a case was excluded from this series. Sixteen of the patients were males, and four were females. Their ages varied from 26 to 73 years and the average age was 54.5 years. A history of excessive alcoholism was present in 15 of the patients. In all patients except one the Wassermann and Kahn tests of the blood were negative. The liver was enlarged in all patients although often the extent of the enlargement was not evident until after clearing of some of the ascitis. Mental disturbances, unrelated to acute alcoholism, and ranging from mild confusion to somnolence or extreme excitement, were frequent

encountered In 4 patients this disturbance was marked, and in 6 others, it was moderate in degree Detectable peripheral edema was present in 9 patients In 10 patients this was described as 4 plus, in 8 as 3 plus, and in only 2, as 2 plus Seven of the patients had required paracentesis before being placed on the regime

The treatment of these patients was essentially the same as has been previously described for the management of the edema of cardiac failure When the patients were admitted to the hospital or as soon as food was tolerated the 'initial diet' was used for the first four to six days and the "full neutral diet" was used thereafter, both in the hospital and after their return home The caloric intake of these patients was not restricted A daily ingestion of 250 Gms of carbohydrate, 75 Gms of protein, and 100 Gms of fat was average for this group Intravenous supplements of 5% dextrose frequently increased the carbohydrate intake by 50 to 100 Gms a day Vitamins (administered orally and parenterally) were given in amounts estimated as necessary to correct any pre-existing deficiency Liver extract was administered intramuscularly to the more seriously ill patients

The fluid intake of all patients exceeded three liters daily Intake and output were recorded as accurately as possible in a general hospital Any correction of errors would increase the amounts recorded Frequently it was necessary to supplement the oral intake of fluid by the intravenous use of 5% dextrose in distilled water, in amounts of one to two liters daily

Ammonium chloride was given in enteric coated tablets in an average dose of 4 Gms daily *Diluted hydrochloric acid* (2 to 3 cc daily in divided doses) was given for varying intervals to many of the patients The mercurial diuretics used in this series were either mercupurin, administered intravenously in 500 cc or 1000 cc of 5% dextrose in distilled water, or less often mercurhydri was given intramuscularly The usual dose of either drug was 2 cc although occasionally 1 cc was given

As already stated, clearing of the ascitis occurred in all but one of the 20 patients The decrease in ascitis was usually proportionate to weight loss, but in some instances the weight loss was less than would be expected with the marked clearing of ascitis due to "shift" of water from the extracellular to intracellular space In the 8 patients whose ascitis was described as 4 plus, or very marked, the average weight loss was 24 4 pounds during the period of clearing of the ascitis, for which an average of 18 9 days were required The patients whose ascitis was 3 plus, cleared their ascitis in an average 13 5 days, accompanied by an average weight loss of 13 0 pounds, whereas ascitis represented a 2 plus accumulation of fluid, cleared their ascites in 9 and 6 days, accompanied by a drop in weight of 11 and 12 pounds, respectively

Little change occurred in the size of the liver during the period of clearing of the ascitis, or subsequent to it This is in contrast to patients whose ascitis is the result of congestive heart failure, and in whom marked decrease in the size of the liver is commonly observed The slight to moderate detectable peripheral edema which was present on admission in 9 patients disappeared during the period of clearing of the ascitis

Improvement in the mental symptoms of these patients after the institution of treatment was striking Initially the degree of their mental disturbance was often sufficiently great that additional nursing at-

tendance was needed. In no instance were these symptoms due to acute alcoholism or to delirium tremens. The improvement of these symptoms did not necessarily parallel clearing of the ascitis, but it did appear to follow more closely upon the institution of a liberal intake of water.

One patient is classed as a failure to this regime. He was a 26-year-old male whose cirrhosis was believed due to a combination of excessive alcoholism and exposure to chemicals. A previous omentopexy had not prevented the re-accumulation of ascitis. The regime did, when enforced, decrease his ascitis from 4 plus to 2 plus, but clearing was never complete. He was the only one of the 20 patients whose mental status did not improve and who quite consistently refused to co-operate. During subsequent "control periods" on a restricted fluid intake, the ascitis fluid reaccumulated rapidly and repeated paracenteses were required.

Fluid intakes of 3,000 to 5,000 cc daily did not produce a gain in weight or increase in ascitis. No initial rehydration gain in weight, such as had been observed in cases with cardio-renal disease, was observed in these 20 cases. In instances where the daily oral intake was low, intravenous infusions of 5 per cent dextrose in distilled water were given in amounts of from one to two liters daily to bring the total intake to the desired amount. In no instance was the administration of these amounts of isotonic dextrose in distilled water followed by any ill effect. The higher daily intakes were enforced orally, or by vein when there was evidence of excessive water vapour loss or marked renal impairment.

Even though the total proteins were low and the albumin-globulin ratio reversed in the blood, and the total protein relatively high in the ascitic fluid, it was possible to remove large amounts of ascitis via the circulation through the manipulation of an ample supply of water.

The mechanism of production of ascitis in portal cirrhosis of the liver is not clearly understood. There have been recent observations that indicate that neither the total protein concentration of the blood nor the level of the albumin fraction controls entirely the accumulation of ascitic fluid. Stasis in the portal system is undoubtedly a factor in the development of the ascitis, but in patients with cirrhosis, fluid may be retained in other parts of the body, even when no ascites is present. The ascitis as well as the peripheral edema of congestive heart failure may be cleared with the low-sodium, acid-ash high fluid regime. Our observations in this duly indicate that the ascitis of portal cirrhosis responds in a similar manner. We feel, therefore, with others that too much emphasis has been placed on the "critical level" of the plasma albumin and on the increased venous pressure in the portal circulation as determining factors in the production of ascites.

Further progress in the treatment of portal cirrhosis of the liver will continue to depend upon its prevention wherever possible as well as its early recognition and the institution of a high carbohydrate, high protein diet, along with vitamin supplements and liver extract. Our observations indicate that a low-sodium, acid-ash diet and a liberal intake of water might well be added to the treatment of patients with chronic parenchymatous liver diseases before the development of ascitis whenever possible and certainly after its appearance.

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